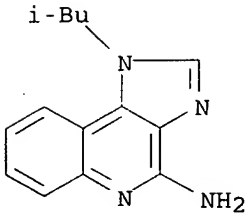
```
      (FILE 'HOME' ENTERED AT 09:24:45 ON 09 MAR 2007)

      FILE 'REGISTRY' ENTERED AT 09:25:17 ON 09 MAR 2007
                EXP ISS-ODN/CN
L1              1 S IMIQUIMOD/CN
L2              1 S RESIQUIMOD/CN
L3              1 S MIZORIBINE/CN

      FILE 'CAPLUS' ENTERED AT 09:26:14 ON 09 MAR 2007
L4            223 S L3/THU
L5             17 S L4 AND CANCER
L6              5 S L5 NOT PY>2004
L7             16 S L2/THU AND CANCER
L8              0 S L7 NOT PY>2004
L9             25 S L2/THU AND INTERFERON
L10            17 S L9 NOT PY>2004
L11            66 S L1/THU AND INTERFERON
L12            34 S L11 NOT PY>2003
L13             3 S L12 AND CANCER

      INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
      AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
      CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
      DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 09:29:54 ON 09 MAR 2007
                SEA OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON
                ---------
                1    FILE BIOSIS
                2    FILE BIOTECHABS
                2    FILE BIOTECHDS
                2    FILE DDFU
                2    FILE DGENE
                2    FILE DRUGU
                1    FILE EMBASE
                1    FILE IFIPAT
                6    FILE MEDLINE
                1    FILE SCISEARCH
                1    FILE TOXCENTER
               37    FILE USPATFULL
                5    FILE USPAT2
                3    FILE WPIDS
                3    FILE WPINDEX
L14              QUE OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON
                ---------

      FILE 'MEDLINE' ENTERED AT 09:31:25 ON 09 MAR 2007
L15             6 S OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON
L16             0 S L15 AND IMIQUIMOD
L17             0 S IMIQUIMOD AND (ISS-ODN)
L18             0 S RESIQUIMOD AND (ISS-ODN)
L19             0 S BIFUNCTIONAL AND (ISS-ODN)

      FILE 'CAPLUS' ENTERED AT 09:33:06 ON 09 MAR 2007
L20             0 S BIFUNCTIONAL AND (ISS-ODN)
L21             4 S BIFUNCTIONAL AND (TOLL-LIKE)
L22         13469 S (INTERFERON(W)(ALPHA OR BETA))
L23          1140 S L22 AND CANCER
L24          9220 S L22 NOT PY>2002
L25           711 S L23 NOT PY>2002
L26            11 S L25 AND EXOGENOUS
L27         20039 S (INTERFERON(1A)(ALPHA OR BETA))
L28          1490 S L27 AND CANCER
L29           949 S L28 NOT PY>2002
L30            14 S L29 AND EXOGENOUS
```

L31 3 S L30 NOT L26

```
=> file registry
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                          ENTRY     SESSION
FULL ESTIMATED COST                                        0.21        0.21

FILE 'REGISTRY' ENTERED AT 09:25:17 ON 09 MAR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:    7 MAR 2007  HIGHEST RN 925547-09-7
DICTIONARY FILE UPDATES:   7 MAR 2007  HIGHEST RN 925547-09-7

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> exp ISS-ODN/cn
E1            1     ISS 610/CN
E2            1     ISS 637/CN
E3            0 --> ISS-ODN/CN
E4            1     ISSAG3, TRANSPOSASE (STREPTOCOCCUS AGALACTIAE STRAIN A909)/C
                    N
E5            2     ISSAG4, TRANSPOSASE ORFA (STREPTOCOCCUS AGALACTIAE STRAIN A9
                    09)/CN
E6            2     ISSAG4, TRANSPOSASE ORFB (STREPTOCOCCUS AGALACTIAE STRAIN A9
                    09)/CN
E7            1     ISSAG5, TRANSPOSASE ORFA (STREPTOCOCCUS AGALACTIAE STRAIN A9
                    09)/CN
E8            1     ISSAG5, TRANSPOSASE ORFB (STREPTOCOCCUS AGALACTIAE STRAIN A9
                    09)/CN
E9            1     ISSAG6, TRANSPOSASE ORFA (STREPTOCOCCUS AGALACTIAE STRAIN A9
                    09)/CN
E10           1     ISSAG7, TRANSPOSASE ORFA (STREPTOCOCCUS AGALACTIAE STRAIN A9
                    09)/CN
E11           5     ISSAG8, TRANSPOSASE (STREPTOCOCCUS AGALACTIAE STRAIN A909)/C
                    N
E12           3     ISSAG9, TRANSPOSASE (STREPTOCOCCUS AGALACTIAE STRAIN A909)/C
                    N

=> s imiquimod/cn
L1            1 IMIQUIMOD/CN

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   99011-02-6  REGISTRY
ED   Entered STN:  09 Nov 1985
CN   1H-Imidazo[4,5-c]quinolin-4-amine, 1-(2-methylpropyl)- (9CI)  (CA INDEX
     NAME)
```

OTHER NAMES:
CN Aldara
CN Imiquimod
CN R 837
CN S 26308
MF C14 H16 N4
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
      (*File contains numerically searchable property data)
    Other Sources: WHO



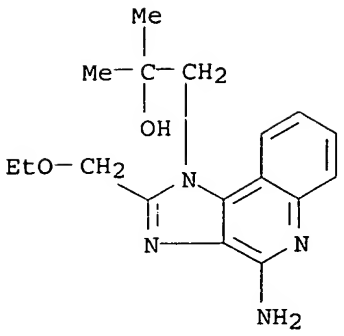
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

404 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
406 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s resiquimod/cn
L2 1 RESIQUIMOD/CN

=> d l2

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN 144875-48-9 REGISTRY
ED Entered STN: 11 Dec 1992
CN 1H-Imidazo[4,5-c]quinoline-1-ethanol, 4-amino-2-(ethoxymethyl)-α,α-dimethyl- (CA INDEX NAME)
OTHER NAMES:
CN 4-Amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol
CN R 848
CN Resiquimod
CN S 28463
DR 171742-32-8, 208711-44-8
MF C17 H22 N4 O2
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, BIOSIS, BIOTECHNO, CA, CAPLUS, CIN, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MRCK*, PHAR, PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
      (*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

164 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
164 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s mizoribine/cn
L3 1 MIZORIBINE/CN

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	19.65	19.86

FILE 'CAPLUS' ENTERED AT 09:26:14 ON 09 MAR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 9 Mar 2007 VOL 146 ISS 11
FILE LAST UPDATED: 7 Mar 2007 (20070307/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

=> s l3/thu
417 L3
865164 THU/RL
L4 223 L3/THU
(L3 (L) THU/RL)

=> d l4 and cancer
'AND' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'
'CANCER' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'

The following are valid formats:

ABS --------- GI and AB
ALL --------- BIB, AB, IND, RE
APPS -------- AI, PRAI
BIB --------- AN, plus Bibliographic Data and PI table (default)
CAN --------- List of CA abstract numbers without answer numbers
CBIB -------- AN, plus Compressed Bibliographic Data
CLASS ------- IPC, NCL, ECLA, FTERM
DALL -------- ALL, delimited (end of each field identified)
DMAX -------- MAX, delimited for post-processing
FAM --------- AN, PI and PRAI in table, plus Patent Family data
FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers;
SCAN must be entered on the same line as the DISPLAY,
e.g., D SCAN or DISPLAY SCAN)
STD --------- BIB, CLASS

IABS -------- ABS, indented with text labels
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
ISTD -------- STD, indented with text labels

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

HIT --------- Fields containing hit terms
HITIND ------ IC, ICA, ICI, NCL, CC and index field (ST and IT)
containing hit terms
HITRN ------- HIT RN and its text modification
HITSTR ------ HIT RN, its text modification, its CA index name, and
its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

To display a particular field or fields, enter the display field codes. For a list of the display field codes, enter HELP DFIELDS at an arrow prompt (=>). Examples of formats include: TI; TI,AU; BIB,ST; TI,IND; TI,SO. You may specify the format fields in any order and the information will be displayed in the same order as the format specification.

All of the formats (except for SAM, SCAN, HIT, HITIND, HITRN, HITSTR, FHITSTR, HITSEQ, FHITSEQ, KWIC, and OCC) may be used with DISPLAY ACC to view a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):ti

L4 ANSWER 1 OF 223 CAPLUS COPYRIGHT 2007 ACS on STN

```
TI   Pteridine derivatives as immunosuppressants, their preparation,
     pharmaceutical compositions, and use in therapy


=> s l4 and cancer
        308330 CANCER
L5          17 L4 AND CANCER

=> s l5 not py>2004
       2817580 PY>2004
L6            5 L5 NOT PY>2004

=> d l6 1-5 ti

L6   ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Inosine monophosphate dehydrogenase inhibitors and prodrugs in the
     treatment of cancer and immune disease

L6   ANSWER 2 OF 5  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Compositions comprising tumor-dendritic Fusion cells, recombinant human
     interleukin 12, antipyretic and immunosuppressant for cancer
     immunotherapy

L6   ANSWER 3 OF 5  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Method for determination of inosine 5'-monophosphate dehydrogenase
     activity in blood during immunosuppressant therapy

L6   ANSWER 4 OF 5  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Preparation of carbocyclic and heterocyclic fused-ring quinolinecarboxylic
     acid immunosuppressive agents

L6   ANSWER 5 OF 5  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Platinum-bredinin complex


=> d l6 1-5 ti abs bib

L6   ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Inosine monophosphate dehydrogenase inhibitors and prodrugs in the
     treatment of cancer and immune disease
AB   The invention provides methods of treating cancer using
     inhibitors of inosine monophosphate dehydrogenase (IMPDH). The IMPDH
     inhibitors are combined with compds. that inhibit cellular processes
     regulated by GTP or ATP. Also provided are prodrugs of the IMPDH
     inhibitor mizoribine and its aglycon. The prodrugs are useful in
     practicing the methods of the invention, including immunosuppressive
     therapy and treatment of cancer by prolonged administration
     without addnl. therapeutic compds.
AN   2004:120731  CAPLUS <<LOGINID::20070309>>
DN   140:157496
TI   Inosine monophosphate dehydrogenase inhibitors and prodrugs in the
     treatment of cancer and immune disease
IN   Carson, Dennis A.; Leoni, Lorenzo M.; Cottam, Howard B.
PA   The Regents of the University of California, USA
SO   PCT Int. Appl., 68 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
PI   WO 2004012746        A2    20040212    WO 2003-US24325         20030801
     WO 2004012746        A3    20040805
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
```

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	AU 2003261354	A1	20040223	AU 2003-261354	20030801
	US 2004127435	A1	20040701	US 2003-632711	20030801
PRAI	US 2002-400583P	P	20020802		
	WO 2003-US24325	W	20030801		

OS MARPAT 140:157496

L6 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
TI Compositions comprising tumor-dendritic Fusion cells, recombinant human interleukin 12, antipyretic and immunosuppressant for cancer immunotherapy
AB The present invention relates to methods and compns. for treating and preventing cancer by administering a therapeutically ED of fusion cells formed by fusion of autologous dendritic cells and autologous non-dendritic cells, in combination with a cytokine or other mol. which stimulates or induces a cytotoxic T cell response and/or a humoral immune response.
AN 2004:119752 CAPLUS <<LOGINID::20070309>>
DN 140:162347
TI Compositions comprising tumor-dendritic Fusion cells, recombinant human interleukin 12, antipyretic and immunosuppressant for cancer immunotherapy
IN Ohno, Tsuneya
PA USA
SO U.S. Pat. Appl. Publ., 38 pp., Cont.-in-part of U.S. Ser. No. 12,134.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004028663	A1	20040212	US 2002-328998	20021224
	US 2002168351	A1	20021114	US 2001-12134	20011022
PRAI	US 2000-242154P	P	20001020		
	US 2001-12134	A2	20011022		

L6 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
TI Method for determination of inosine 5'-monophosphate dehydrogenase activity in blood during immunosuppressant therapy
AB The invention concerns the determination of IMP dehydrogenase(IMDPH) activity in
blood during cancer therapeutic IMDPH suppression treatment by using IMP substrate and NAD cofactor; and measuring spectrophotometrically one of the reaction components during formation of xanthosine 5'-monophosphate and NADH directly or after cleavage of the xanthosine 5'-monophosphate. Leukocytes are isolated from blood and resuspended in the plasma of the same patient; after sonication, substrate and cofactor are added; the mixture is incubated at 37°C, followed by centrifugation. Using HPLC separation, the quantity of xanthosine 5'-monophosphate is determined at 260 nm. Blood of cancer patients or patients undergoing organ transplantation are assayed by the method. Immunosuppressants used in the therapy are: mycophenolic acid, mycophenolate mofetil, tiazofurine, ribavirin, mizoribine, or VX-497. The invention also concerns a test kit for performing the IMDPH blood assay.
AN 1999:624652 CAPLUS <<LOGINID::20070309>>
DN 131:225481

TI Method for determination of inosine 5'-monophosphate dehydrogenase activity in blood during immunosuppressant therapy
IN Albrecht, Wolfgang; Bungers, Eva; Martin, Wolfgang; Guserle, Richard
PA Merckle G.m.b.H., Germany
SO Ger. Offen., 18 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19811313	A1	19990923	DE 1998-19811313	19980316
PRAI	DE 1998-19811313		19980316		

L6 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
TI Preparation of carbocyclic and heterocyclic fused-ring quinolinecarboxylic acid immunosuppressive agents
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I, II; R1, R2 = H, Cl, Br, CF3, alkyl; R3 = Ph, PhO, PhS (un)substituted PhNH, heterocyclyl, etc.; X = YCH2, CH2Y, CH2CH2Y, YCH2CH2, etc.; Y = (un)substituted CH2, O, S, (un)substituted NH; Z1-Z3 = N, (un)substituted CH] (e.g., I; R1 = 6-F, R2 = H, R3 = 4-MeC6H4, X = CH2CH2, Z1-Z3 = CH) [III; Q1, Q2 = S, (un)substituted NH, (un)substituted CH] (IV; Q3, Q4 = N, C; R11 = H, F, Cl, Br, CF3, alkyl), useful as immunosuppressants for the treatment of organ transplantation rejection, graft vs. host diseases, autoimmune diseases, cancer, chronic inflammatory diseases, etc., are prepared and I-, II-, III-, and IV-containing formulations presented.
AN 1995:846523 CAPLUS <<LOGINID::20070309>>
DN 123:256538
TI Preparation of carbocyclic and heterocyclic fused-ring quinolinecarboxylic acid immunosuppressive agents
IN Magolda, Ronald Louis; Pitts, William John; Jacobson, Irina Cipora; Behrens, Carl Henry; Orwat, Michael James; Batt, Douglas Guy
PA Du Pont Merck Pharmaceutical Co., USA
SO PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9506640	A1	19950309	WO 1994-US9463	19940826
	W: AU, BR, CA, CN, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5428040	A	19950627	US 1993-114712	19930831
	CA 2170349	A1	19950309	CA 1994-2170349	19940826
	AU 9476358	A	19950322	AU 1994-76358	19940826
	AU 690140	B2	19980423		
	EP 716652	A1	19960619	EP 1994-926555	19940826
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	HU 74585	A2	19970128	HU 1996-501	19940826
	JP 09501442	T	19970210	JP 1995-508162	19940826
	RU 2133740	C1	19990727	RU 1996-107400	19940826
	IL 110821	A	19970415	IL 1994-110821	19940830
	ZA 9406658	A	19960229	ZA 1994-6658	19940831
	US 5639759	A	19970617	US 1995-411251	19950327
	FI 9600933	A	19960228	FI 1996-933	19960228

```
     NO 9600811           A     19960429    NO 1996-811           19960228
     US 5874441           A     19990223    US 1997-820222        19970318
     US 6110910           A     20000829    US 1998-195366        19981118
PRAI US 1993-114712       A     19930831
     WO 1994-US9463       W     19940826
     US 1995-411251       A3    19950327
     US 1997-820222       A3    19970318
OS   MARPAT 123:256538

L6   ANSWER 5 OF 5  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Platinum-bredinin complex
AB   An aqueous mixture of 100 mg cis-dichlorodiammine platinum(II) and 110 mg AgNO3
     was stirred overnight at room temperature, filtered, 0.1 N HCl added to the
     filtrate, the mixture filtered, 850 mg bredinin added to the resulting
     diaquodiammine platinum(II) nitrate solution, and the whole stirred 1 wk at
     room temperature in the dark to give, after chromatog. over SiO2 gel, 150 mg
     Pt-bredinin complex.  An inhibitory ratio of the product was 20 μg
     Pt/mL against L5178Y cancer cells.
AN   1980:568561  CAPLUS <<LOGINID::20070309>>
DN   93:168561
TI   Platinum-bredinin complex
PA   Toyo Jozo Co., Ltd., Japan
SO   Jpn. Kokai Tokkyo Koho, 3 pp.
     CODEN: JKXXAF
DT   Patent
LA   Japanese
FAN.CNT 1
     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
PI   JP 55047696           A     19800404    JP 1978-120673          19780929
PRAI JP 1978-120673        A     19780929


=> s l2/thu and cancer
           164 L2
        865164 THU/RL
           119 L2/THU
                 (L2 (L) THU/RL)
        308330 CANCER
L7          16 L2/THU AND CANCER

=> s l7 not py>2004
       2817580 PY>2004
L8             0 L7 NOT PY>2004

=> s l2/thu and interferon
           164 L2
        865164 THU/RL
           119 L2/THU
                 (L2 (L) THU/RL)
         75697 INTERFERON
L9          25 L2/THU AND INTERFERON

=> s l9 not py>2004
       2817580 PY>2004
L10         17 L9 NOT PY>2004

=> d l10 1-17 ti

L10  ANSWER 1 OF 17  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Resiquimod, a new immune response modifier from the family of
     imidazoquinolinamines, inhibits allergen-induced Th2 responses, airway
     inflammation and airway hyper-reactivity in mice
```

L10 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Imiquimod and resiquimod in a mouse model: adjuvants for DNA vaccination by particle-mediated immunotherapeutic delivery

L10 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Resiquimod is a modest adjuvant for HIV-1 gag-based genetic immunization in a mouse model

L10 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Randomized, single-blind, placebo-controlled study of topical application of the immune response modulator resiquimod in healthy adults

L10 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI The novel synthetic immune response modifier R-848 (resiquimod) shifts human allergen-specific CD4+ TH2 lymphocytes into IFN-γ-producing cells

L10 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Inhibition of IgE production by the imidazoquinoline resiquimod in nonallergic and allergic donors

L10 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Dendritic cell maturation and IL-12 synthesis induced by the synthetic immune-response modifier S-28463

L10 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway

L10 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Imiquimod and resiquimod as novel immunomodulators

L10 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Clearance of infection with Mycobacterium bovis BCG in mice is enhanced by treatment with S28463 (R-848), and its efficiency depends on expression of wild-type Nramp1 (resistance allele)

L10 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: A pilot study

L10 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Current recommendations for the treatment of genital herpes

L10 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI S-28463: treatment of hepatitis C, interferon inducer

L10 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Gel formulations for topical drug delivery

L10 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Cytokine induction in hairless mouse and rat skin after topical application of the immune response modifiers imiquimod and S-28463

L10 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Effect of a novel topical immunomodulator, S-28463, on keratinocyte cytokine gene expression and production

L10 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI 1-Substituted, 2-substituted 1H-imidazo[4,5-c]quinolin-4-amines as antiviral and antitumor agents and inducers of biosynthesis of interferon

=> d l10 1 2 9 11 13 17 ti abs bib

L10 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Resiquimod, a new immune response modifier from the family of imidazoquinolinamines, inhibits allergen-induced Th2 responses, airway inflammation and airway hyper-reactivity in mice
AB Background: Allergen-induced sensitization and airway disease are the results of adverse immune reactions against environmental antigens that may be prevented or inhibited by immune modifying strategies. Objective: To investigate the effects of the novel immune response modifier resiquimod (R-848), from the family of imidazol-derivates, in a marine model of allergen-mediated Th2-immune responses and concomitant airway inflammation and airway hyper-reactivity. Methods: BALB/c mice were systemically sensitized with ovalbumin (OVA) on days 1 and 14 and challenged with OVA aerosol on days 28 and 29. R-848 was applied intranasally to sensitized animals once prior to the first allergen airway challenge, on day 27. Results: A single application of R-848 significantly reduced nos. of eosinophils and lymphocytes in bronchoalveolar lavage fluid and inhibited mucus gland hyperplasia, compared with sensitized and challenged controls. Associated with the decrease in airway inflammation, single intranasal treatment with R-848 abolished the development of airway hyper-reactivity after allergen sensitization and airway challenges. Addnl., Th2-cytokine production in lung tissues from sensitized and R-848-treated animals was reduced, whereas IL-12 and IFN-γ production was increased, compared with non-treated sensitized mice. Conclusions: These data indicate that R-848 effectively inhibits allergen-induced airway inflammation and hyper-reactivity by modulation of increased Th2-immune responses.
AN 2004:765477 CAPLUS <<LOGINID::20070309>>
DN 142:106842
TI Resiquimod, a new immune response modifier from the family of imidazoquinolinamines, inhibits allergen-induced Th2 responses, airway inflammation and airway hyper-reactivity in mice
AU Quarcoo, D.; Weixler, S.; Joachim, R. A.; Stock, P.; Kallinich, T.; Ahrens, B.; Hamelmann, E.
CS Department of Pediatric Pneumology and Immunology, Charite-Humboldt University, Berlin, Germany
SO Clinical and Experimental Allergy (2004), 34(8), 1314-1320
CODEN: CLEAEN; ISSN: 0954-7894
PB Blackwell Publishing Ltd.
DT Journal
LA English
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Imiquimod and resiquimod in a mouse model: adjuvants for DNA vaccination by particle-mediated immunotherapeutic delivery
AB Imiquimod, an immune response modifier and inducer of cytokines in vitro and in vivo, has been shown to have potent antiviral and antitumor activity and to act as an adjuvant for protein vaccination. We have undertaken studies in mice to investigate the potential of imiquimod and resiquimod to adjuvant DNA vaccination. These imidazoquinolines were administered by s.c. injection at the vaccination site immediately after particle-mediated immunotherapeutic delivery of plasmid DNA using a gene gun. Imiquimod was found to increase the number and maturation status of dendritic cells in draining lymph nodes, and to enhance antigen-specific CD4+ and CD8+ T cell responses, as assessed by analyses of clonal expansion, and the quantity and kinetics of cytokine production from these cells in lymph nodes and spleens collected after vaccination. A more substantial increase in IFN-γ-producing, compared with IL-4-producing CD4+ T cells suggested that imiquimod biased the immune response towards a predominance of Th1 cells. The analog resiquimod was found to be to produce a similar Th1 biased immune response with a 10-fold

reduced dose compared with imiquimod. Collectively, these studies suggest that both imiquimod and resiquimod may be suitable adjuvants for therapeutic DNA vaccines requiring induction of potent cytotoxic T cell responses.

AN 2004:285023 CAPLUS <<LOGINID::20070309>>
DN 141:138769
TI Imiquimod and resiquimod in a mouse model: adjuvants for DNA vaccination by particle-mediated immunotherapeutic delivery
AU Thomsen, Lindy L.; Topley, Peter; Daly, Maria G.; Brett, Sara J.; Tite, John P.
CS Department of Immunotherapeutics, GlaxoSmithKline Medicines Research Centre, Hertfordshire, SG1 2NY, UK
SO Vaccine (2004), 22(13-14), 1799-1809
CODEN: VACCDE; ISSN: 0264-410X
PB Elsevier Science Ltd.
DT Journal
LA English
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Imiquimod and resiquimod as novel immunomodulators
AB A review. Augmenting the host's natural immune response to viruses by the administration of exogenous cytokines such as interferon-α (IFN-α) is a strategy increasingly employed in antiviral therapeutics. Enhancing the release of endogenous cytokines is, however, an alternative approach. The imidazoquinolinamines imiquimod and resiquimod have demonstrated potency as inducers of IFN-α and other cytokines both in vitro and in vivo. Cytokine gene activation is mediated via the signal transducer and activator of transcription 1 (STAT-1) and involves the transcription factors NFκB and α4F1. Antiviral activity has been demonstrated against a variety of viruses, and clin. efficacy has been demonstrated against genital warts, herpes genitalis and molluscum contagiosum. Imiquimod is administered as a 5% cream (Aldara) and has been licensed for the treatment of anogenital warts in immunocompetent patients. Complete clearance of warts has been observed in up to half of treated patients with only local side effects reported. Resiquimod can be administered topically but also exists as an oral formulation. The range of potential infections for which these agents may have clin. utility includes chronic hepatitis C virus infection and Kaposi's sarcoma. In addition, the imidazoquinolinamines may find roles in the therapy of cancers and as vaccine adjuvants.
AN 2002:32301 CAPLUS <<LOGINID::20070309>>
DN 136:272485
TI Imiquimod and resiquimod as novel immunomodulators
AU Dockrell, D. H.; Kinghorn, G. R.
CS Department of Infectious Diseases, Royal Hallamshire Hospital, Sheffield, UK
SO Journal of Antimicrobial Chemotherapy (2001), 48(6), 751-755
CODEN: JACHDX; ISSN: 0305-7453
PB Oxford University Press
DT Journal; General Review
LA English
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

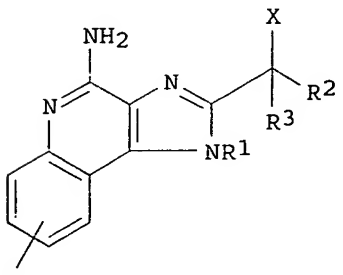
L10 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: A pilot study
AB Resiquimod (R-848), a topically active immune response modifier, induced production of interferon-α and interleukin-12 in cultured blood mononuclear cells and decreased genital herpes recurrences in an animal model. In this study, 52 patients with frequently recurrent genital herpes applied topical resiquimod gel 0.01% (twice or thrice

weekly) or 0.05% (once or twice weekly) or vehicle gel to herpes lesions for 3 wk. During the 6-mo observation period after treatment, median days to first recurrence in the pooled resiquimod group was 169 days, compared with 57 days for the vehicle group (P =.0058). In all, 32% of resiquimod-treated patients completed the observation period without a recurrence, compared with 6% of vehicle-treated patients (P =.039). Resiquimod 0.05% twice weekly produced dose-limiting inflammation at the lesion sites, but the other regimens were well tolerated. Application of resiquimod to genital herpes lesions appeared to reduce the frequency of recurrences.

AN 2001:561869 CAPLUS <<LOGINID::20070309>>
DN 135:313221
TI Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: A pilot study
AU Spruance, Spotswood L.; Tyring, Stephen K.; Smith, Michael H.; Meng, Tze-Chiang
CS Department of Medicine, School of Medicine, University of Utah, Salt Lake City, UT, 84132, USA
SO Journal of Infectious Diseases (2001), 184(2), 196-200
CODEN: JIDIAQ; ISSN: 0022-1899
PB University of Chicago Press
DT Journal
LA English
RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI S-28463: treatment of hepatitis C, interferon inducer
AB A review with 22 refs. on the synthesis, pharmacol., and clin. studies of S-28463, an interferon inducer with antiviral activity.
AN 1999:555369 CAPLUS <<LOGINID::20070309>>
DN 132:87525
TI S-28463: treatment of hepatitis C, interferon inducer
AU Graul, A.; Castaner, J.
CS Prous Science, Barcelona, 08080, Spain
SO Drugs of the Future (1999), 24(6), 622-627
CODEN: DRFUD4; ISSN: 0377-8282
PB Prous Science
DT Journal; General Review
LA English
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI 1-Substituted, 2-substituted 1H-imidazo[4,5-c]quinolin-4-amines as antiviral and antitumor agents and inducers of biosynthesis of interferon
GI



I

AB 1-Substituted, 2-substituted 1H-imidazo[4,5-c]-quinolin-4-amines I [wherein R1 is selected from the group consisting of: hydroxyalkyl of one to about six carbon atoms and alkoxyalkyl wherein the alkoxy moiety is of one to about four carbon atoms and the alkyl moiety is of one to about six carbon atoms; R2 and R3 are independently selected from the group consisting of hydrogen and alkyl of one to about four carbon atoms; X is selected from the group consisting of alkoxy of one to about four carbon atoms, alkoxyalkyl wherein the alkoxy moiety is of one to about four carbon atoms and the alkyl moiety is of one to about four carbon atoms, hydroxyalkyl of one to about four carbon atoms, and hydroxy; and R is selected from the group consisting of hydrogen, straight chain or branched chain alkoxy of one to about four carbon atoms, halogen, and straight chain or branched chain alkyl of one to about four carbon atoms; or a pharmaceutically acceptable acid addition salt thereof] are disclosed. These compds. function as antiviral agents, they induce biosynthesis of interferon, and they inhibit tumor formation in animal models. This invention also provides intermediates for preparing such compds., pharmaceutical compns. containing such compds., and pharmacol. methods of using such compds. I inhibited Herpes simplex virus type II lesions in guinea pigs and were also active against vesicular stomatitis virus in vitro. Interferon-α induction in human cells by I: at dose concentration of, e.g., 0.50 μg/mL, α reference units/mL of up to 2500 were observed Inhibition of MC-26 tumors in mice by I: at dose of 30 mg/kg, number of colonies as low as 123 ± 31 vs. 385 ± 31 for control were observed

AN 1995:420800 CAPLUS <<LOGINID::20070309>>
DN 123:83363
TI 1-Substituted, 2-substituted 1H-imidazo[4,5-c]quinolin-4-amines as antiviral and antitumor agents and inducers of biosynthesis of interferon
IN Gerster, John F.; Crooks, Stephen L.; Lindstrom, Kyle J.
PA Minnesota Mining and Manufacturing Co., USA
SO U.S., 26 pp. Cont.-in-part of U.S. Ser. No. 838,475, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5389640	A	19950214	US 1992-938295	19920828
	CA 2104782	A1	19920902	CA 1992-2104782	19920220
	CA 2104782	C	20010807		
	EP 872478	A2	19981021	EP 1998-105754	19920220
	EP 872478	A3	19981104		
	EP 872478	B1	20021218		
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE				
	CA 2289219	C	20030520	CA 1992-2289219	19920220
	ZA 9201540	A	19921125	ZA 1992-1540	19920228
	IL 114570	A	19961031	IL 1992-114570	19920301
	US 5605899	A	19970225	US 1994-353802	19941212
	US 5741909	A	19980421	US 1997-789264	19970128
	US 5977366	A	19991102	US 1998-60010	19980414
	US 6348462	B1	20020219	US 1999-386486	19990827
	US 2002115861	A1	20020822	US 2001-974038	20011009
	US 6465654	B2	20021015		
	US 2003119861	A1	20030626	US 2002-238661	20020910
	US 6608201	B2	20030819		
	US 2003212270	A1	20031113	US 2003-436905	20030513
	US 6686472	B2	20040203		
	US 2004122231	A1	20040624	US 2003-731826	20031209
	US 6790961	B2	20040914		
PRAI	US 1991-662926	B2	19910301		
	US 1991-687326	B2	19910418		

```
     US 1992-838475        B2     19920219
     CA 1992-2104782       A3     19920220
     EP 1992-906763        A3     19920220
     IL 1992-101110        A3     19920301
     US 1992-938295        A3     19920828
     US 1994-353802        A3     19941212
     US 1997-789264        A3     19970128
     US 1998-60010         A3     19980414
     US 1999-386486        A1     19990827
     US 2001-974038        A3     20011009
     US 2002-238661        A3     20020910
     US 2003-436905        A3     20030513
OS   MARPAT 123:83363


=> s l1/thu and interferon
          406 L1
       865164 THU/RL
          337 L1/THU
                (L1 (L) THU/RL)
        75697 INTERFERON
L11        66 L1/THU AND INTERFERON

=> s l11 not py>2003
      3948023 PY>2003
L12        34 L11 NOT PY>2003

=> s L12 and cancer
       308330 CANCER
L13         3 L12 AND CANCER

=> d L13 1-3 ti

L13  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   The use of toll-like receptor-7 agonist in the treatment of basal cell
     carcinoma: an overview

L13  ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Imiquimod 5% cream (Aldara)

L13  ANSWER 3 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   A phase I clinical trial of imiquimod, an oral interferon
     inducer, administered daily


=> d L13 1-3 ti abs bib

L13  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   The use of toll-like receptor-7 agonist in the treatment of basal cell
     carcinoma: an overview
AB   A review.  Basal cell carcinoma (BCC) is a subtype of nonmelanoma skin
     cancer (NMSC), with an increasing incidence worldwide.  Currently,
     excision of the tumor with histol. control is the standard therapy.  However,
     high incidence rates have led to concern about the economic burden imposed
     by BCC management in many countries.  Imiquimod is a member of a novel
     class of immune response modifiers (IRM), which works by using the
     toll-like receptor (TLR)-7.  Although the exact mode of action is so far
     unknown, it is suggested to induce the expression of different cytokines
     like interleukin (IL)-1, IL-6, IL-12, interferon (IFN)-α
     and tumor necrosis factor (TNF)-α, which stimulate or enhance both
     the innate immune system and the cell-mediated immune response.  Preclin.
     studies have indicated the potential of this TLR-7 agonist for the
     treatment of precancers and tumors in humans.  A number of Phase II trials
     have demonstrated the efficacy of imiquimod for the treatment of BCC,
```

although the most appropriate dosing regimen is being confirmed in Phase III studies. Imiquimod 5% cream for the treatment of mainly superficial BCC appears to be an effective and well-tolerated treatment option.

AN 2004:63952 CAPLUS <<LOGINID::20070309>>
DN 140:121944
TI The use of toll-like receptor-7 agonist in the treatment of basal cell carcinoma: an overview
AU Stockfleth, E.; Trefzer, U.; Garcia-Bartels, C.; Wegner, T.; Schmook, T.; Sterry, W.
CS Department of Dermatology, University Hospital Charite, Berlin, D-10117, Germany
SO British Journal of Dermatology, Supplement (2003), 149(66), 53-56
CODEN: BJDSA9; ISSN: 0366-077X
PB Blackwell Publishing Ltd.
DT Journal; General Review
LA English
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
TI Imiquimod 5% cream (Aldara)
AB A review with 23 refs. Imiquimod is a novel synthetic mol. with potent immune-modifying activities. Formulated in a 5% vanishing cream as Aldara, this self-applied therapy has shown good efficacy and safety in the treatment of external genital and perianal warts caused by human papillomavirus (HPV) infection (Condyloma acuminata). The mol. does not demonstrate direct antiviral activity, but through induction of cytokines results in immune-based resolution of wart tissue and reduction of viral burden.

Phase III trials of imiquimod have demonstrated that patients who experience complete clearance of either new or recalcitrant warts tend to remain clear, possibly related to Th1 immune recognition and memory. Self-application, good tolerability and a unique mechanism of action combine to make imiquimod a reasonable first-line therapy for genital warts. The effects of imiquimod on immune function suggest several potential uses. Preclin. studies of infection with herpes simplex virus (HSV), cutaneous leishmaniasis, Rift Valley Fever virus and vesiculostomatitis virus have shown reduced viral persistence, reduced recurrence (HSV) and diminished pathol. (Leishmania donovani). In a murine tumor model using the FCB bladder cancer cell line, imiquimod behaves as a potent adjuvant leading to immune-based tumor cell eradication and immunity against subsequent FCB cell challenge. The ability of imiquimod to induce significant production of interferon alpha (IFN-α) by monocytes/macrophages suggests that diseases responsive to recombinant interferon therapy, such as basal cell carcinoma, may be reasonable clin. targets. The induction of tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ) and interleukin-12 (IL-12) leads to inhibition of IL-5, with animal models demonstrating immune deviation away from Th2 immune responses. The observation that several patients with hepatitis C infection and eosinophilia showed normalization of elevated eosinophil counts in association with oral imiquimod therapy encourages further exploration of the immune modifying properties of this novel mol. This review is focused on the use of imiquimod for the treatment of external genital and perianal warts.

AN 1998:198531 CAPLUS <<LOGINID::20070309>>
DN 128:316756
TI Imiquimod 5% cream (Aldara)
AU Slade, H. B.; Owens, M. L.; Tomai, M. A.; Miller, R. L.
CS 3M Pharmaceuticals, St Paul, MN, 55144-1000, USA
SO Expert Opinion on Investigational Drugs (1998), 7(3), 437-449
CODEN: EOIDER; ISSN: 1354-3784
PB Ashley Publications
DT Journal; General Review

LA English
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
TI A phase I clinical trial of imiquimod, an oral interferon inducer, administered daily
AB Imiquimod is an orally active interferon inducer with anti-tumor activity in exptl. animals. In this study the tolerability, toxicity and biol. effects of daily oral imiquimod administration were investigated in 21 patients with refractory cancer. Patients were treated with doses of 25 mg, 50 mg, 100 mg or 200 mg on a projected 112 day course. Only three patients completed the course, all at the 50 mg dose. Treatment toxicities were dose related and mainly comprised flu-like symptoms, nausea and lymphopenia. Of the 21 patients, five received dose redns. and in five treatment was discontinued because of treatment-related toxicity. The biol. activity of imiquimod was confirmed by significant and sustained rises in peripheral blood mononuclear cell (PBMC) 2-5A synthetase (2-5AS) levels at all doses. At 100 mg and 200 mg these occurred within the first 24 h of administration. Levels of neopterin and β2-microglobulin (β2M) were also significantly elevated when assessed after three weeks' treatment. Interferon production was not demonstrated within the first 24 h of the initial dose but, following repeated doses, ten of the patients developed detectable serum interferon concns. with a maximum value of 5600 IU mL-1 recorded. Administration of imiquimod did not have any significant effect on serum levels of tumor necrosis factor (TNF) or interleukin 1 (IL-1), nor did it lead to development of detectable levels of antibodies to interferon. One mixed clin. response was observed after 4 wk' treatment at 100 mg in a patient with renal cell cancer. Daily administration of imiquimod causes activation of the interferon production system but at higher doses results in unacceptable toxicity. Further investigation of imiquimod as an interferon-inducing agent in cancer patients is suggested at either the lower dose levels or employing alternative dosing schedules.
AN 1996:707118 CAPLUS <<LOGINID::20070309>>
DN 126:14415
TI A phase I clinical trial of imiquimod, an oral interferon inducer, administered daily
AU Savage, P.; Horton, V.; Moore, J.; Owens, M.; Witt, P.; Gore, M. E.
CS Department Medicine, Royal Marsden Hospital, London, SW6 6JJ, UK
SO British Journal of Cancer (1996), 74(9), 1482-1486
CODEN: BJCAAI; ISSN: 0007-0920
PB Stockton
DT Journal
LA English

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	77.41	97.27

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-10.92	-10.92

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE, AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 09:29:54 ON 09 MAR 2007

68 FILES IN THE FILE LIST IN STNINDEX

```
Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s oligonucleotide and (ISS-ODN) and interferon
           1    FILE BIOSIS
           2    FILE BIOTECHABS
           2    FILE BIOTECHDS
           2    FILE DDFU
           2    FILE DGENE
           2    FILE DRUGU
           1    FILE EMBASE
  29 FILES SEARCHED...
           1    FILE IFIPAT
           6    FILE MEDLINE
           1    FILE SCISEARCH
           1    FILE TOXCENTER
          37    FILE USPATFULL
           5    FILE USPAT2
  64 FILES SEARCHED...
           3    FILE WPIDS
           3    FILE WPINDEX

  15 FILES HAVE ONE OR MORE ANSWERS,    68 FILES SEARCHED IN STNINDEX

L14   QUE OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON

=> file medline
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 1.89      99.16

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                   ENTRY    SESSION
CA SUBSCRIBER PRICE                                 0.00     -10.92

FILE 'MEDLINE' ENTERED AT 09:31:25 ON 09 MAR 2007

 FILE LAST UPDATED: 8 Mar 2007 (20070308/UP).  FILE COVERS 1950 TO DATE.

  All regular MEDLINE updates from November 15 to December 16 have been
  added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R))
  and 2007 tree numbers.

  The annual reload will be available in early 2007.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification...

=> s oligonucleotide and (ISS-ODN) and interferon
         57990 OLIGONUCLEOTIDE
          2702 ISS
          2685 ODN
            38 ISS-ODN
                 (ISS(W)ODN)
         97513 INTERFERON
L15          6 OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON

=> d l15 1-6 ti

L15  ANSWER 1 OF 6     MEDLINE on STN
TI   Suppression of allergic response by CpG motif oligodeoxynucleotide-house-
     dust mite conjugate in animal model of allergic rhinitis.
```

L15 ANSWER 2 OF 6 MEDLINE on STN
TI Dendritic cells and HIV infection: activating dendritic cells to boost immunity.

L15 ANSWER 3 OF 6 MEDLINE on STN
TI CpG-C ISS-ODN activation of blood-derived B cells from healthy and chronic immunodeficiency virus-infected macaques.

L15 ANSWER 4 OF 6 MEDLINE on STN
TI Molecular and cellular mechanisms of protective immunity to coccidioidomycosis.

L15 ANSWER 5 OF 6 MEDLINE on STN
TI CpG-C immunostimulatory oligodeoxyribonucleotide activation of plasmacytoid dendritic cells in rhesus macaques to augment the activation of IFN-gamma-secreting simian immunodeficiency virus-specific T cells.

L15 ANSWER 6 OF 6 MEDLINE on STN
TI A minimal human immunostimulatory CpG motif that potently induces IFN-gamma and IFN-alpha production.

=> d l15 1-6 ti abs bib

L15 ANSWER 1 OF 6 MEDLINE on STN
TI Suppression of allergic response by CpG motif oligodeoxynucleotide-house-dust mite conjugate in animal model of allergic rhinitis.
AB BACKGROUND: Although there have been many therapeutic options for allergic disease, the true allergen desensitization remains a challenging goal. The classic immunotherapy has a limited efficacy, is inconvenient, and has a risk of anaphylaxis. Recent reports revealed that immunostimulatory DNA sequences (ISS-oligdeoxynucleotide [ODN], CpG motif) act as a strong Th1 response-inducing adjuvants and that DNA-based vaccination might be an effective therapeutic option. In this study, we investigate whether ISS-ODN/Dermatophagoides farinae (Der f) conjugate has antiallergic effects in the allergic rhinitis mouse model, sensitive to house-dust mites. Der f is the most common allergen-inducing allergic rhinitis in Korea. METHODS: C57BL/6 mice were sensitized with crude extract of Der f. After injection of ISS-ODN or ISS-ODN/Der f conjugate, several parameters of allergic response were evaluated. RESULTS: Scratching and sneezing symptoms and eosinophilic infiltration into nasal mucosa were suppressed by injection with ISS-ODN only and ISS-ODN/Der f conjugate. Interleukin-5 level was decreased and interferon gamma level was increased in nasal lavage fluid by injection of ISS-ODN/Der f conjugate. Der f-specific immunoglobulin E was decreased by injection of ISS-ODN or Der f / ISS-ODN conjugate; however, these were not statistically significant. Transforming growth factor beta1 secreted by cultured splenocyte was increased significantly in ISS-ODN/Der f conjugate group. CONCLUSION: These results suggest ISS-ODN/Der f conjugate induces an antiallergic effect and induces an increase in transforming growth factor beta1 level in the allergic rhinitis model using Der f allergen. Allergic response developed by Der f allergen could be more effectively reduced by injection with ISS-ODN/Der f conjugate than by injection with ISS-ODN only.
AN 2006262068 MEDLINE <<LOGINID::20070309>>
DN PubMed ID: 16686392
TI Suppression of allergic response by CpG motif oligodeoxynucleotide-house-dust mite conjugate in animal model of allergic rhinitis.
AU Mo Ji-Hun; Park Seok-Won; Rhee Chae-Seo; Takabayashi Kenji; Lee Seung Sin; Quan Song-Hua; Kim In-Sang; Min Il Yang-Gi; Raz Eyal; Lee Chul Hee
CS Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National

University College of Medicine, Seoul, Korea.
SO American journal of rhinology, (2006 Mar-Apr) Vol. 20, No. 2, pp. 212-8.
Journal code: 8807268. ISSN: 1050-6586.
CY United States
DT (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 200611
ED Entered STN: 12 May 2006
Last Updated on STN: 19 Dec 2006
Entered Medline: 29 Nov 2006

L15 ANSWER 2 OF 6 MEDLINE on STN
TI Dendritic cells and HIV infection: activating dendritic cells to boost immunity.
AB Dendritic cells (DCs) are white blood cells that coordinate innate and adaptive immunity. They are distributed within epithelia and mucosal-associated lymphoid tissues, positioned to entrap incoming pathogens or vaccines. Human immunodeficiency virus (HIV) and the non-human primate equivalent (SIV) exploit DCs to amplify infection, underscoring the need to harness strategies that promote presentation of virus by DCs to stimulate potent anti-viral immunity instead of virus transmission. Two main subsets of DCs need to be considered: myeloid (MDC) and plasmacytoid (PDC) subsets. Using the SIV-macaque system to advance oral vaccine research, we examined macaque PDC and MDC biology, identifying ways to activate DCs and boost antiviral immunity. Immunostimulatory oligodeoxyribonucleotides (ISS-ODNs) stimulated PDC/MDC mixtures to up-regulate co-stimulatory molecule expression and to secrete both IFN-alpha and IL-12. Additionally, ISS-ODNs augmented SIV-specific IFN-gamma responses induced by virus-bearing DCs. ISS-ODN-driven DC activation is being pursued to improve oral/nasopharyngeal mucosal vaccines and therapies against HIV.
AN 2006247894 MEDLINE <<LOGINID::20070309>>
DN PubMed ID: 16672547
TI Dendritic cells and HIV infection: activating dendritic cells to boost immunity.
AU Teleshova N; Kenney J; Robbiani M
CS Center for Biomedical Research, Population Council, 1230 York Avenue, New York, NY 10021, USA.
NC DE015512 (NIDCR)
DE016256 (NIDCR)
DE016534 (NIDCR)
HD041752 (NICHD)
P01S AI052048 (NIAID)
R01S AI040877 (NIAID)
R21S AI060405 (NIAID)
RR00164 (NCRR)
U19 AI065413 (NIAID)
SO Advances in dental research, (2006) Vol. 19, No. 1, pp. 36-41. Electronic Publication: 2006-04-01.
Journal code: 8802131. E-ISSN: 1544-0737.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LA English
FS Dental Journals
EM 200607
ED Entered STN: 5 May 2006
Last Updated on STN: 19 Jul 2006
Entered Medline: 18 Jul 2006

L15 ANSWER 3 OF 6 MEDLINE on STN
TI CpG-C ISS-ODN activation of blood-derived B cells from healthy and chronic immunodeficiency virus-infected macaques.
AB Cytosine-phosphate-guanine class C (CpG-C) immunostimulatory sequence oligodeoxynucleotides (ISS-ODNs) activate human B cells and dendritic cells (DCs), properties that suggest potential use as a novel adjuvant to enhance vaccine efficacy. After demonstrating that the CpG-C ISS -ODN C274 activates macaque DCs, we examined in vitro activation of macaque B cells by C274 as a prelude to evaluation of this molecule as an adjuvant in the testing of candidate human immunodeficiency virus vaccines in the rhesus macaque-simian immunodeficiency virus (SIV) model. C274 induced macaque CD20(+) B cells to proliferate more strongly than CD40 ligand or CpG-B ISS-ODN. C274 enhanced B cell survival; increased viability was most evident after 3-7 days of culture. Increased expression of CD40, CD80, and CD86 by B cells was apparent within 24 h of exposure to C274 and persisted for up to 1 week. C274-stimulated, B cell-enriched and peripheral blood mononuclear cell suspensions from naive and immunodeficiency virus-infected monkeys secreted several cytokines [e.g., interleukin (IL)-3, IL-6, IL-12, interferon-alpha] and chemokines [e.g., monocyte chemoattractant protein-1/CC chemokine ligand 2 (CCL2), macrophage-inflammatory protein-1alpha/CCL3, IL-8/CXC chemokine ligand 8]. In comparison, exposure of macaque B cells to SIV had minimal impact on surface phenotype, despite inducing cytokine and chemokine production in cells from infected and uninfected animals. These observations emphasize the need to identify strategies to optimally boost immune function, as immunodeficiency viruses themselves only partially activate B cells and DCs. The ability of C274 to stimulate B cells and DCs in healthy and infected monkeys suggests its possible use as a broad-acting adjuvant to be applied in the rhesus macaque model for the development of preventative and therapeutic vaccines.
AN 2006059047 MEDLINE <<LOGINID::20070309>>
DN PubMed ID: 16443827
TI CpG-C ISS-ODN activation of blood-derived B cells from healthy and chronic immunodeficiency virus-infected macaques.
AU Teleshova N; Kenney J; Williams V; Van Nest G; Marshall J; Lifson J D; Sivin I; Dufour J; Bohm R; Gettie A; Pope M
CS Population Council, 1230 York Avenue, New York, NY 10021, USA.
NC DE016256 (NIDCR)
N01-CO-12400 (NCI)
R01 AI040877 (NIAID)
R21 AI060405 (NIAID)
RR00164 (NCRR)
SO Journal of leukocyte biology, (2006 Feb) Vol. 79, No. 2, pp. 257-67.
Journal code: 8405628. ISSN: 0741-5400.
CY United States
DT (COMPARATIVE STUDY)
(IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LA English
FS Priority Journals
EM 200605
ED Entered STN: 31 Jan 2006
Last Updated on STN: 12 May 2006
Entered Medline: 11 May 2006

L15 ANSWER 4 OF 6 MEDLINE on STN
TI Molecular and cellular mechanisms of protective immunity to coccidioidomycosis.
AB Coccidioides immitis is endemic in the soil of the desert Southwest. It causes a respiratory infection that is usually mild, but can last months and may disseminate beyond the lung. Disseminated infections can be fatal

or require life-long therapy. Development of an effective vaccine may be a successful method of preventing serious disease. In this paper, we show that immunostimulatory-oligodeoxynucleotides (ISS-ODN) are an effective adjuvant for a recombinant coccidioidal protein known as antigen 2/proline rich antigen. Protective immunity induced by this ISS-ODN-based vaccine requires IL-12, interferon -gamma and MHC Class II-restricted T-cells. Cytotoxic CD8 T-cells are not required. This study elucidates the mechanisms needed to elicit successful immunity against coccidioidomycosis, and holds promise for development of an effective coccidioidal vaccine against coccidioidomycosis.

AN 2005697159 MEDLINE <<LOGINID::20070309>>
DN PubMed ID: 16181709
TI Molecular and cellular mechanisms of protective immunity to coccidioidomycosis.
AU Kirkland Theo N; Raz Eyal; Datta Sandip K
CS The Department of Pathology and Medicine, University of California-San Diego School of Medicine, 9500 Gilman Drive, La Jolla, CA 92093, USA.. tkirkland@ucsd.edu
NC R01 GM 066119 (NIGMS)
R37 AI 19149 (NIAID)
SO Vaccine, (2006 Jan 23) Vol. 24, No. 4, pp. 495-500. Electronic Publication: 2005-08-15.
Journal code: 8406899. ISSN: 0264-410X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 200604
ED Entered STN: 31 Dec 2005
Last Updated on STN: 26 Apr 2006
Entered Medline: 25 Apr 2006

L15 ANSWER 5 OF 6 MEDLINE on STN
TI CpG-C immunostimulatory oligodeoxyribonucleotide activation of plasmacytoid dendritic cells in rhesus macaques to augment the activation of IFN-gamma-secreting simian immunodeficiency virus-specific T cells.
AB There are two principle subsets of dendritic cells (DCs); CD11c(+)CD123(-) myeloid DCs (MDCs) and CD11c(-)CD123(+) plasmacytoid DCs (PDCs). DC activation via TNF-TNFRs (e.g., CD40L) and TLRs (e.g., immunostimulatory oligodeoxyribonucleotides (ISS-ODNs)) is crucial for maximal stimulation of innate and adaptive immunity. Macaque DC biology is being studied to improve HIV vaccines using the SIV macaque model. Using lineage (Lin) markers to exclude non-DCs, Lin(-)HLA-DR(+)CD11c(+)CD123(-) MDCs and Lin(-)HLA-DR(+)CD11c(-)CD123(+) PDCs were identified in the blood of uninfected macaques and healthy macaques infected with SIV or simian-human immunodeficiency virus. Overnight culture of DC-enriched Lin-depleted cells increased CD80 and CD86 expression. IL-12 production and CD80/CD86 expression by MDC/PDC mixtures was further enhanced by CD40L and ISS-ODN treatment. A CpG-B ISS-ODN increased CD80/CD86 expression by PDCs, but resulted in little IFN-alpha secretion unless IL-3 was added. In contrast, a CpG-C ISS-ODN and aldrithiol-2-inactivated (AT-2) SIV induced considerable PDC activation and IFN-alpha release without needing exogenous IL-3. The CpG-C ISS-ODN also stimulated IL-12 release (unlike AT-2 SIV) and augmented DC immunostimulatory activity, increasing SIV-specific T cell IFN-gamma production induced by AT-2 SIV-presenting MDC/PDC-enriched mixtures. These data highlight the functional capacities of MDCs and PDCs in naive as well as healthy, infected macaques, revealing a promising CpG-C ISS-ODN-driven DC activation strategy that boosts immune function to augment preventative and therapeutic vaccine efficacy.

AN 2004369784 MEDLINE <<LOGINID::20070309>>
DN PubMed ID: 15265893
TI CpG-C immunostimulatory oligodeoxyribonucleotide activation of plasmacytoid dendritic cells in rhesus macaques to augment the activation of IFN-gamma-secreting simian immunodeficiency virus-specific T cells.
AU Teleshova Natalia; Kenney Jessica; Jones Jennifer; Marshall Jason; Van Nest Gary; Dufour Jason; Bohm Rudolf; Lifson Jeffrey D; Gettie Agegnehu; Pope Melissa
CS Center for Biomedical Research, Population Council, New York, NY 10021, USA.
NC R01 AI40877 (NIAID)
R21 AI52060 (NIAID)
RR00164 (NCRR)
SO Journal of immunology (Baltimore, Md. : 1950), (2004 Aug 1) Vol. 173, No. 3, pp. 1647-57.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200411
ED Entered STN: 28 Jul 2004
Last Updated on STN: 3 Nov 2004
Entered Medline: 2 Nov 2004

L15 ANSWER 6 OF 6 MEDLINE on STN
TI A minimal human immunostimulatory CpG motif that potently induces IFN-gamma and IFN-alpha production.
AB Recent reports have shown that immunostimulatory sequences (ISS) containing CpG motifs have minimal length requirements (>/=12 bases) for the exertion of immune-enhancing function upon mammalian cells. Herein we demonstrate that short ISS (5-7 bases), which exhibit no activity on their own, induce IFN-gamma and IFN-alpha secretion from human peripheral blood mononuclear cells when adsorbed to the surface of cationic poly(D,L-lactide-co-glycolide) microparticles (cPLGA). Utilizing this technique, we discovered a minimal ISS sequence for induction of IFN-gamma and IFN-alpha from human cells: 5'-TCGXX-3'. These short ISS/cPLGA formulations targeted PDC in similar fashion to longer ISS ODN, the activity of which does not require (but is enhanced by) cPLGA. PDC stimulated with short ISS/cPLGA responded with enhanced uptake of ISS and elevated production of cytokines, including IFN-alpha. However, ISS-responsive B cells did not respond to short ISS/cPLGA, underlining the plasmacytoid dendritic cell selectivity of this formulation. These results describe a novel technique for formulating active, but very short, ISS oligodeoxynucleotide that allows for the dissection and characterization of minimal immunostimulatory CpG motifs.
AN 2003350780 MEDLINE <<LOGINID::20070309>>
DN PubMed ID: 12884285
TI A minimal human immunostimulatory CpG motif that potently induces IFN-gamma and IFN-alpha production.
AU Fearon Karen; Marshall Jason D; Abbate Christi; Subramanian Sandhya; Yee Priscilla; Gregorio Josh; Teshima Glen; Ott Gary; Tuck Stephen; Van Nest Gary; Coffman Robert L
CS Dynavax Technologies Corporation, Berkeley, CA 94710, USA.
SO European journal of immunology, (2003 Aug) Vol. 33, No. 8, pp. 2114-22.
Journal code: 1273201. ISSN: 0014-2980.
CY Germany: Germany, Federal Republic of
DT (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

```
EM   200309
ED   Entered STN: 29 Jul 2003
     Last Updated on STN: 30 Sep 2003
     Entered Medline: 29 Sep 2003


=> s l15 and imiquimod
           822 IMIQUIMOD
L16          0 L15 AND IMIQUIMOD

=> s imiquimod and (ISS-ODN)
           822 IMIQUIMOD
          2702 ISS
          2685 ODN
            38 ISS-ODN
                 (ISS(W)ODN)
L17          0 IMIQUIMOD AND (ISS-ODN)

=> s resiquimod and (ISS-ODN)
            46 RESIQUIMOD
          2702 ISS
          2685 ODN
            38 ISS-ODN
                 (ISS(W)ODN)
L18          0 RESIQUIMOD AND (ISS-ODN)

=> s bifunctional and (ISS-ODN)
          6994 BIFUNCTIONAL
          2702 ISS
          2685 ODN
            38 ISS-ODN
                 (ISS(W)ODN)
L19          0 BIFUNCTIONAL AND (ISS-ODN)

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    2.49     101.65

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                    0.00     -10.92

FILE 'CAPLUS' ENTERED AT 09:33:06 ON 09 MAR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 9 Mar 2007  VOL 146 ISS 11
FILE LAST UPDATED: 7 Mar 2007  (20070307/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:
```

http://www.cas.org/infopolicy.html

```
=> s bifunctional and (ISS-ODN)
         20852 BIFUNCTIONAL
          2486 ISS
          3353 ODN
            52 ISS-ODN
                 (ISS(W)ODN)
L20           0 BIFUNCTIONAL AND (ISS-ODN)

=> s bifunctional and (Toll-like)
         20852 BIFUNCTIONAL
          8154 TOLL
        779044 LIKE
          7141 TOLL-LIKE
                 (TOLL(W)LIKE)
L21           4 BIFUNCTIONAL AND (TOLL-LIKE)

=> d l21 1-4 ti

L21  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Polynucleotide marker genes and their expression for diagnosis of
     endotoxemia-related conditions in horses

L21  ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Design of bifunctional siRNAs: Combining immunostimulation and
     gene-silencing in one single siRNA molecule

L21  ANSWER 3 OF 4  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   MyD88-dependent and -independent signaling by IL-1 in neurons probed by
     bifunctional Toll/IL-1 receptor domain/BB-loop mimetics

L21  ANSWER 4 OF 4  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Gene expression profiles in the diagnosis and treatment of Alzheimer's
     disease


=> d l21 1-4 ti abs bib

L21  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Polynucleotide marker genes and their expression for diagnosis of
     endotoxemia-related conditions in horses
AB   The invention discloses isolated endotoxemia marker polynucleotides
     selected from any one of 163 different polynucleotide sequences, or
     variants thereof.  Endotoxemia (also called septic shock or septic
     syndrome)-related conditions are diagnosed in a test subject by aberrant
     expression of at least one of the endotoxemia markers or variants thereof.
     Of practical use is the early diagnosis of disease, determining those animals
at
     risk of developing endotoxemia, monitoring of an animal's immune response
     to the disease, and the enablement of better treatments.  The
     differentially expressed markers were identified by GeneChip anal. using
     Affymetrix technol. of blood obtained from normal horses and from horses
     with clin. evidence of an endotoxemia-related condition.  A gene signature
     of 159 genes demonstrates a specificity of 99% for toxemia in a population
     sample size of over 850 individuals.  Of particular interest is the
     diagnosis of laminitis in hoofed animals, including horses.
AN   2007:61320  CAPLUS <<LOGINID::20070309>>
DN   146:182524
TI   Polynucleotide marker genes and their expression for diagnosis of
     endotoxemia-related conditions in horses
IN   Brandon, Richard Bruce; Thomas, Mervyn Rees
PA   Athlomics Pty. Ltd., Australia
```

SO PCT Int. Appl., 602pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007006091	A1	20070118	WO 2006-AU970	20060707

PI
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRAI US 2005-696776P P 20050707
RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
TI Design of bifunctional siRNAs: Combining immunostimulation and gene-silencing in one single siRNA molecule
AB Active suppression of T lymphocyte activation can limit the efficacy of immune surveillance and immunotherapy. Here the authors have explored the possibility of designing bifunctional small interfering RNAs (siRNAs) capable of inducing innate immunity through Toll-like receptors and simultaneously inhibiting the expression of immunosuppressive factors. Using interleukin (IL) 10 as a model, the authors found that liposomal delivery of IL10 siRNAs could efficiently activate the expression of cytokines (e.g. TNF-α, IL6, and IL12) and interferons (e.g. IFN-α) in peripheral blood mononuclear cells (PBMCs) and immature monocyte-derived dendritic cells (iMoDCs). Moreover, the designed siRNAs inhibited IL10 gene expression. Transfection of iMoDCs with either chemical or in vitro transcribed IL10 siRNAs induced their differentiation into mature MoDCs (mMoDCs) characterized by the expression of costimulatory mols. CD80/CD86 and the chemokine receptor CCR7. Lipid delivery of either chemical synthesized or T7-transcribed immunostimulatory siRNAs induced cytokine production However, in contrast to chemical synthesized siRNAs, electroporation of in vitro transcribed siRNAs also induced cytokine production in iMoDCs. Interestingly, IL10 siRNA-transfected iMoDCs were capable of enhancing the response of allogeneic T cells, providing support for the rational design of bifunctional siRNAs as immune modulating therapy.
AN 2006:1331123 CAPLUS <<LOGINID::20070309>>
TI Design of bifunctional siRNAs: Combining immunostimulation and gene-silencing in one single siRNA molecule
AU Furset, Gro; Sioud, Mouldy
CS Department of Immunology, Molecular Medicine Group, Norwegian Radium Hospital, University of Oslo, Oslo, N-0310, Norway
SO Biochemical and Biophysical Research Communications (2007), 352(3), 642-649
CODEN: BBRCA9; ISSN: 0006-291X
PB Elsevier
DT Journal
LA English
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
TI MyD88-dependent and -independent signaling by IL-1 in neurons probed by bifunctional Toll/IL-1 receptor domain/BB-loop mimetics
AB Interleukin (IL)-1β is a pluripotent proinflammatory cytokine that signals through the type-I IL-1 receptor (IL-1RI), a member of the Toll-like receptor family. In hypothalamic neurons, binding of IL-1β to IL-1RI mediates transcription-dependent changes that depend on the recruitment of the cytosolic adaptor protein myeloid differentiation primary-response protein 88 (MyD88) to the IL-1RI/IL-1 receptor accessory protein (IL-1RAcP) complex through homomeric Toll/IL-1 receptor (TIR)-TIR interactions. Through design and synthesis of bifunctional TIR mimetics that disrupt the interaction of MyD88 with the IL-1RI/IL-1RAcP complex, the authors analyzed the involvement of MyD88 in the signaling of IL-1β in anterior hypothalamic neurons. The authors show here that IL-1β-mediated activation of the protein tyrosine kinase Src depended on a MyD88 interaction with the IL-1RI/IL-1RAcP complex. The activation of the protein kinase Akt/PKB depended on the recruitment of the p85 subunit of PI3K to IL-1RI and independent of MyD88 association with the IL-1RI/IL-1RAcP complex. These bifunctional TIR-TIR mimetics represent a class of low-mol.-weight compds. with both an antiinflammatory and neuroprotective potential. These compds. have the potential to inhibit the MyD88-dependent proinflammatory actions of IL-1β, while permitting the potential neuronal survival supporting actions mediated by the MyD88-independent activation of the protein kinase Akt.
AN 2006:459889 CAPLUS <<LOGINID::20070309>>
DN 145:6252
TI MyD88-dependent and -independent signaling by IL-1 in neurons probed by bifunctional Toll/IL-1 receptor domain/BB-loop mimetics
AU Davis, Christopher N.; Mann, Enrique; Behrens, M. Margarita; Gaidarova, Svetlana; Rebek, Mitra; Rebek, Julius, Jr.; Bartfai, Tamas
CS The Harold L. Dorris Neurological Institute and Department of Molecular and Integrative Neurosciences, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Proceedings of the National Academy of Sciences of the United States of America (2006), 103(8), 2953-2958
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
OS CASREACT 145:6252
RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
TI Gene expression profiles in the diagnosis and treatment of Alzheimer's disease
AB Genes showing altered patterns of expression in the brain that are associated with the neurol. changes found in Alzheimer's disease and that can be used in the early diagnosis of the disease, including the incipient form of the disease, are identified. The methods and kits of the invention utilize a set of genes and their encoded proteins that are shown to be correlated with incipient Alzheimer's disease.
AN 2005:902703 CAPLUS <<LOGINID::20070309>>
DN 143:272498
TI Gene expression profiles in the diagnosis and treatment of Alzheimer's disease
IN Landfield, Philip W.; Porter, Nada M.; Chen, Kuey Chu; Geddes, James; Blalock, Eric
PA University of Kentucky Research Foundation, USA
SO PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DT Patent
LA English

```
FAN.CNT 1
     PATENT NO.            KIND   DATE        APPLICATION NO.          DATE
     ---------------       ----   --------    --------------------     --------
PI   WO 2005076939          A2    20050825    WO 2005-US3668           20050209
     WO 2005076939          A3    20060706
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SM
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
PRAI US 2004-542281P         P     20040209


=> d his

     (FILE 'HOME' ENTERED AT 09:24:45 ON 09 MAR 2007)

     FILE 'REGISTRY' ENTERED AT 09:25:17 ON 09 MAR 2007
                EXP ISS-ODN/CN
L1            1 S IMIQUIMOD/CN
L2            1 S RESIQUIMOD/CN
L3            1 S MIZORIBINE/CN

     FILE 'CAPLUS' ENTERED AT 09:26:14 ON 09 MAR 2007
L4          223 S L3/THU
L5           17 S L4 AND CANCER
L6            5 S L5 NOT PY>2004
L7           16 S L2/THU AND CANCER
L8            0 S L7 NOT PY>2004
L9           25 S L2/THU AND INTERFERON
L10          17 S L9 NOT PY>2004
L11          66 S L1/THU AND INTERFERON
L12          34 S L11 NOT PY>2003
L13           3 S L12 AND CANCER

     INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
     AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
     CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
     DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 09:29:54 ON 09 MAR 2007
                SEA OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON
               ---------
               1   FILE BIOSIS
               2   FILE BIOTECHABS
               2   FILE BIOTECHDS
               2   FILE DDFU
               2   FILE DGENE
               2   FILE DRUGU
               1   FILE EMBASE
               1   FILE IFIPAT
               6   FILE MEDLINE
               1   FILE SCISEARCH
               1   FILE TOXCENTER
              37   FILE USPATFULL
               5   FILE USPAT2
               3   FILE WPIDS
               3   FILE WPINDEX
L14             QUE OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON
               ---------
```

```
     FILE 'MEDLINE' ENTERED AT 09:31:25 ON 09 MAR 2007
L15             6 S OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON
L16             0 S L15 AND IMIQUIMOD
L17             0 S IMIQUIMOD AND (ISS-ODN)
L18             0 S RESIQUIMOD AND (ISS-ODN)
L19             0 S BIFUNCTIONAL AND (ISS-ODN)

     FILE 'CAPLUS' ENTERED AT 09:33:06 ON 09 MAR 2007
L20             0 S BIFUNCTIONAL AND (ISS-ODN)
L21             4 S BIFUNCTIONAL AND (TOLL-LIKE)

=> log hold
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    25.68     127.33

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -3.12     -14.04

 SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 09:34:17 ON 09 MAR 2007

Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:SSPTAEXO1623

PASSWORD:
 * * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'CAPLUS' AT 10:37:47 ON 09 MAR 2007
FILE 'CAPLUS' ENTERED AT 10:37:47 ON 09 MAR 2007
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)s

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    25.68     127.33

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -3.12     -14.04

=> s (interferon(w)(alpha or beta))
         75697 INTERFERON
       1671236 ALPHA
       1439661 BETA
L22      13469 (INTERFERON(W)(ALPHA OR BETA))

=> s l22 and cancer
        308330 CANCER
L23       1140 L22 AND CANCER

=> s l32 not py>2002
L32 NOT FOUND
The L-number entered could not be found.  To see the definition
of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s l22 not py>2002
       4999482 PY>2002
```

```
L24        9220 L22 NOT PY>2002

=> s l23 not py>2002
     4999482 PY>2002
L25         711 L23 NOT PY>2002

=> s l25 and exogenous
       94609 EXOGENOUS
L26           11 L25 AND EXOGENOUS

=> d l26 1-11 ti

L26  ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Effect of transfection with human interferon-β
     gene entrapped in cationic multilamellar liposomes in combination with
     5-fluorouracil on the growth of human esophageal cancer cells in
     vitro

L26  ANSWER 2 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Eradication of intraperitoneal and distant tumor by adenovirus-mediated
     interferon-β  gene therapy is attributable to
     induction of systemic immunity

L26  ANSWER 3 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Anticancer drug-induced kidney disorders: Incidence, prevention and
     management

L26  ANSWER 4 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Increasing efficiency of transduction by inhibition of β-interferon
     action and inhibition of neovascularization of tumors with angiostatin
     expression vectors

L26  ANSWER 5 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Endocrine-mediated mechanisms of fatigue during treatment with
     interferon-α

L26  ANSWER 6 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Sensitization of renal carcinoma to radiation using alpha interferon
     (IFNA) gene transfection

L26  ANSWER 7 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Cytokine-induced autoimmune disorders

L26  ANSWER 8 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Modulation of the immunostimulating effect of autologous tumor vaccine by
     anti-TGF-β antibody and  interferon-α  on
     murine MBT-2 bladder cancer

L26  ANSWER 9 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Neuroimmunotherapy of human neoplasms with melatonin and antitumor
     cytokines

L26  ANSWER 10 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   In vitro modulation of the invasive and metastatic potentials of human
     renal cell carcinoma by interleukin-2 and/or interferon-
     alpha gene transfer

L26  ANSWER 11 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Tumor-specific lysis of human renal cell carcinomas by tumor-infiltrating
     lymphocytes: modulation of recognition through retroviral transduction of
     tumor cells with interleukin 2 complementary DNA and exogenous
     α interferon treatment
```

=> d l26 4 5 6 8 9 11 ti abs bib

L26 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
TI Increasing efficiency of transduction by inhibition of β-interferon action and inhibition of neovascularization of tumors with angiostatin expression vectors
AB A method of increasing the effectiveness of virus-mediated gene therapy by inhibiting β-interferon function is described. The method is specifically intended for use with adenovirus-based vectors. Inhibitors include antibodies to interferon β or antisense DNA or ribozymes inhibiting gene expression. The method can be used to improve effectiveness of gene therapy of genetic diseases and of cancers. Methods for the treatment of neovascularization-related diseases, for examples, cancer, by the production in vivo of angiostatin, which inhibits the formation of new blood vessels are also described. In particular embodiments, this is accomplished by transduction of macrophages ex vivo with a GM-CSF gene, thereby inducing the secretion of macrophage metalloelastase, which converts plasminogen to angiostatin. The transduced macrophages, when administered, naturally home to tumor sites to effectively localize the therapeutic effect. Expts. in which macrophages were transformed with reporter gene expression constructs demonstrated that neutralization of interferon β in the medium with monoclonal antibodies increased the level of expression of the reporter. Addition of exogenous β-interferon decreased levels of expression.
AN 1998:352956 CAPLUS <<LOGINID::20070309>>
DN 129:24138
TI Increasing efficiency of transduction by inhibition of β-interferon action and inhibition of neovascularization of tumors with angiostatin expression vectors
IN Fidler, Isaiah J.; Dong, Zhongyun; Kumar, Rakesh
PA Board of Regents, the University of Texas System, USA
SO PCT Int. Appl., 182 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9822605	A1	19980528	WO 1997-US21475	19971119
	W: CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2275438	A1	19980528	CA 1997-2275438	19971119
	EP 963440	A1	19991215	EP 1997-950669	19971119
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001505205	T	20010417	JP 1998-523953	19971119
PRAI	US 1996-31330P	P	19961120		
	WO 1997-US21475	W	19971119		

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
TI Endocrine-mediated mechanisms of fatigue during treatment with interferon-α
AB A review with 95 refs. Fatigue occurs in more than 70% of patients treated with interferon-α (IFN-α) and is the most problematic toxicity associated with IFN-based immunotherapy. Abundant evidence suggests that immune-mediated endocrine disease occurs during IFN-α therapy, which may contribute to the etiol. of fatigue. Autoimmune thyroid disease is a well-recognized consequence of IFN-α therapy and may be mediated by the induction of IFN-γ production by lymphocytes. Administration of exogenous IFN-γ has been associated with upregulation of class II major histocompatibility antigens in

the thyroid and the development of thyroiditis. Interferon-. alpha. also stimulates the production of interleukin-6; both interleukin-6 and IFN-γ have specific effects on thyrocyte function. There also is evidence suggesting that IFN-α initiates a cytokine cascade that effects the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes, thus affecting regulation of glucocorticoid and sex steroid hormone secretion, but the clin. significance of these observations has not been established. Although endocrine disease will not explain the occurrence of fatigue symptoms in all patients, there is clear evidence that hormonal deficiency syndromes occur in a relatively large portion of patients receiving systemic IFN-α therapy. Most importantly, the possibility of hypothyroidism must be considered; however, diagnosis of hypothyroidism in cancer patients is complicated by the occurrence of the "sick euthyroid syndrome.". Clin. recommendations for assessment and treatment of IFN-α-induced fatigue are offered. Most importantly, measurements of TSH and antithyroid autoantibodies should be used to evaluate thyroid status. Acknowledging the limitations of current clin. data, adrenal- and gonadal-axis dys-function also must be considered in patients with IFN-α-induced fatigue.

AN 1998:146116 CAPLUS <<LOGINID::20070309>>
DN 128:242673
TI Endocrine-mediated mechanisms of fatigue during treatment with interferon-α
AU Jones, T. Hugh; Wadler, Scott; Hupart, Kenneth H.
CS Departments of Medicine and Pharmacology, Royal Hallamshire Hospital and University of Sheffield, Sheffield, UK
SO Seminars in Oncology (1998), 25(1, Suppl. 1), 54-63
CODEN: SOLGAV; ISSN: 0093-7754
PB W. B. Saunders Co.
DT Journal; General Review
LA English
RE.CNT 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
TI Sensitization of renal carcinoma to radiation using alpha interferon (IFNA) gene transfection
AB The rationale for this study was that local delivery of interferon -alpha (IFN-α) by gene transfection may be of value during radiotherapy. To investigate the feasibility of this approach, cells of the human renal carcinoma cell line R11 were transfected with the IFNA gene and evaluated for radiation responses in vitro by clonogenic assays. R11 cells expressing IFN-α after gene transfection were more sensitive to radiation than R11 control cells (SF2 = 0.33 and 0.51, resp.). In addition to increasing radiosensitivity, IFNA gene transfection slowed cellular growth and reduced the plating efficiency in clonogenic assays. The addition of exogenous rhIFN-α to cells at different times relative to irradiation showed that its presence during the postirradn. period was critical for radiosensitization, but repair of sublethal damage did not seem to be affected. No apoptosis of R11 cells was found 1-5 days after exposure to 2-25 Gy with or without IFN-α. Extensive formation of multinuclear giant cells was present beginning 2 days after irradiation; however, IFN-α did not cause any major alterations in the yield of radiation-induced giant cells. These studies suggest that gene transfection might be an effective means of delivering IFN-α for clin. use in radiotherapy of cancer.
AN 1997:708948 CAPLUS <<LOGINID::20070309>>
DN 128:31917
TI Sensitization of renal carcinoma to radiation using alpha interferon (IFNA) gene transfection
AU Gyljuasen, Randi G.; Belldegrun, Arie; Tso, Cho-Lea; Withers, H. Rodney; McBride, William H.
CS Dep. Radiation Oncol., Univ. California, Los Angeles, CA, 90095, USA

SO Radiation Research (1997), 148(5), 443-448
CODEN: RAREAE; ISSN: 0033-7587
PB Radiation Research Society
DT Journal
LA English
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
TI Modulation of the immunostimulating effect of autologous tumor vaccine by anti-TGF-β antibody and interferon-α on murine MBT-2 bladder cancer
AB Our aims were to: a) elucidate whether MBT-2 cells, lethally irradiated or nonirradiated, express TGF-β1 mRNA and secrete TGF-β1 protein, and b) to investigate whether the adverse effects from IRMBT-2-secreting TGF-β1 in the tumor vaccine can be abrogated by exogenous addition of monoclonal anti-TGF-β1 antibody and/or IFN-α. Using the Northern hybridization anal. and the two-antibody sandwich ELISA, we demonstrate that both irradiated IRMBT-2 and nonirradiated MBT-2 cells secrete TGF-β1. The effect of anti-TGF-β and/or IFN-α were studied by an in vitro splenocyte proliferation assay and in vivo tumor rechallenge study on day 17-TBM. Both IRMBT-2 and splenocytes from day 17-TBM secrete TGF-β1 which can express suppression of the proliferation of the splenocytes from day 17-TBM. This suppression can be partially reversed by the simultaneous addition of both anti-TGF-β and IFN-α, either alone being insufficient. The result of the in vivo tumor rechallenge study on day 17-TBM reveals that a lower tumor outgrowth incidence can be obtained in groups of mice treated with postoperative vaccination with anti-TGF-β modified tumor vaccine with or without an addnl. administration of IFN-α. Apart from TGF-β, MBT-2 cells, both irradiated and nonirradiated, may also secrete other suppressive factors that adversely downregulate the immune response of TBM which can not then be adequately reversed by IFN-α.
AN 1997:307397 CAPLUS <<LOGINID::20070309>>
DN 126:342432
TI Modulation of the immunostimulating effect of autologous tumor vaccine by anti-TGF-β antibody and interferon-α on murine MBT-2 bladder cancer
AU Tzai, Tzong-Shin; Shiau, Ai-Li; Lin, Chein-Sheng; Wu, Chao-Liang; Shinn-Nan Lin, Johnny
CS Department of Urology, Medical College, National Cheng Kung University, Tainan, Taiwan
SO Anticancer Research (1997), 17(2A), 1073-1078
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
TI Neuroimmunotherapy of human neoplasms with melatonin and antitumor cytokines
AB The biol. and antitumor activities of cytokines have appeared to be modulated by the psycho neuroendocrine system, mainly by the pineal hormone melatonin (MLT) and opioid peptides. In particular, MLT has been seen to amplify IL-2 anticancer action and to reduce its toxicity. The rationale of MLT use in association with IL-2 cancer immunotherapy may be summarized, as follows: (1) amplification of IL-2 biol. activity by enhancing TH2 lymphocyte response and by antagonizing macrophage-mediated suppressive events; (2) inhibition of production of tumor growth factors, which stimulate cancer cell proliferation by counteracting lymphocyte-mediated tumor cell destruction; (3) maintenance of a circadian rhythm of MLT, which is often altered in human neoplasms and influenced by

cytokine exogenous injection. The neuro immunotherapy with s.c. low-dose IL-2 (3 million IU/day) and pharmacol. doses of MLT (40 mg/day orally) in the evening has appeared to be effective in tumor histotypes resistant either to IL-2 alone, or to chemotherapy. At present, 230 patients with advanced solid tumors and life expectancy less than 6 mo have been treated. Objective tumor regressions were in 44 patients (18%), mainly in patients with lung cancer, hepatocarcinoma, cancer of pancreas, gastric cancer, colon cancer . A survival longer than 1 yr was achieved in 95/230 (41%) patients. Toxicity was low in all patients, who were treated as home therapy. Moreover, preliminary data suggest that MLT synergizes also with TNF and interferon alpha, by reducing their toxicity.

AN 1997:36277 CAPLUS <<LOGINID::20070309>>
DN 126:58707
TI Neuroimmunotherapy of human neoplasms with melatonin and antitumor cytokines
AU Lissoni, P.
CS Division of Radiation Oncology, San Gerardo Hospital, Milan, Italy
SO International Journal of Thymology (1996), 4(Suppl. 1), 84-87
CODEN: IJTYEI; ISSN: 0943-1675
PB Thymus Medizinischer Fachbuchverlag
DT Journal
LA English

L26 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
TI Tumor-specific lysis of human renal cell carcinomas by tumor-infiltrating lymphocytes: modulation of recognition through retroviral transduction of tumor cells with interleukin 2 complementary DNA and exogenous α interferon treatment
AB Two cytotoxic effector cell populations were isolated from a patient with renal cell carcinoma. The tumor-infiltrating lymphocytes comprised a population of highly specific, major histocompatibility complex-restricted, cytotoxic T lymphocytes (CTL). An autologous non-major histocompatibility complex-restricted lymphokine-activated killer (LAK) cell population was generated by culturing the peripheral blood lymphocytes with high doses of recombinant interleukin 2 (rIL-2). The capacity of these two effector cell types to lyse cytokine-modulated autologous tumor cells was compared in vitro. A complementary DNA for rIL-2 was introduced into the tumor cells by retroviral transduction, and tumor cells secreting low doses of rIL-2 were isolated. The CTL recognition of these tumor cells was enhanced, compared to unmodified tumor cells, whereas LAK cell recognition was unchanged or slightly reduced. Pretreatment of tumor cells with exogenous α interferon led to an up-regulation of some major histocompatibility complex class I mols. and to slightly better recognition by the CTL; little effect on LAK cell recognition was observed CTL were 50-150 fold more effective than LAK cells in lysing autologous tumor cell lines or clones modulated with both rIL-2 and α interferon. The assessment of a patient's cytotoxic immune capacity directed against genetically modified autologous tumor cells in vitro provides important insight for cytokine-mediated gene therapy of cancer.
AN 1993:624146 CAPLUS <<LOGINID::20070309>>
DN 119:224146
TI Tumor-specific lysis of human renal cell carcinomas by tumor-infiltrating lymphocytes: modulation of recognition through retroviral transduction of tumor cells with interleukin 2 complementary DNA and exogenous α interferon treatment
AU Schendel, Dolores J.; Gansbacher, Bernd
CS Inst. Immunol., Ludwig-Maximilians-Univ., Munich, 8000/2, Germany
SO Cancer Research (1993), 53(17), 4020-5
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English

```
=> s (interferon(1a)(alpha or beta))
         75697 INTERFERON
       1671236 ALPHA
       1439661 BETA
L27      20039 (INTERFERON(1A)(ALPHA OR BETA))

=> s l27 and cancer
        308330 CANCER
L28       1490 L27 AND CANCER

=> s l28 not py>2002
       4999482 PY>2002
L29        949 L28 NOT PY>2002

=> s l29 and exogenous
         94609 EXOGENOUS
L30         14 L29 AND EXOGENOUS

=> s l30 not L26
L31          3 L30 NOT L26

=> d l31 1-3 ti

L31  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Towards defining roles and relationships for tenascin-C and TGFβ-1 in
     the normal and neoplastic urinary bladder

L31  ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Interferon-γ reduces tumor-induced Ia- macrophage-mediated
     suppression: role of prostaglandin E2, Ia, and tumor necrosis
     factor-α

L31  ANSWER 3 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Constitutive production of interleukin 6 by ovarian cancer cell
     lines and by primary ovarian tumor cultures


=> d l31 ti abs bib

L31  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Towards defining roles and relationships for tenascin-C and TGFβ-1 in
     the normal and neoplastic urinary bladder
AB   Tenascin-C (TN-C) is an extracellular matrix glycoprotein expressed along
     epithelial/stromal boundaries during tissue remodeling events, such as
     those that occur during morphogenesis, wound healing, and tumor invasion.
     Using clin. specimens and a range of in vitro models that simulate
     homeostasis, wound healing, and malignant progression, this study sought
     to establish the patterns of TN-C expression in normal and neoplastic
     bladder and to determine the role of exogenous transforming growth
     factor β-1 (TGFβ-1), interleukin-4 (IL-4), basic fibroblast
     growth factor (bFGF), tumor necrosis factor alpha (TNFα ),
     and interferon gamma (IFNγ) in the induction of TN-C
     expression by bladder uro-epithelial cells.  The findings indicate that
     normal urothelial cells may express TN-C, with both TGFβ-1 and IL-4
     able to induce expression.  TN-C was not expressed in neoplastic
     urothelium, although both TN-C and TGFβ-1 may be involved in tissue
     remodeling during papillary tumor formation and invasion.  Furthermore,
     the urothelium of high-grade papillary tumors and carcinoma in situ
     specimens exhibited little TGFβ-1 immunoreactivity, compared with the
     urothelium of low-grade tumors and normal specimens, suggesting an association
     between TGFβ-1 expression and urothelial differentiation.  A tumor
     invasion model, in which established bladder cancer cell lines
     were seeded onto a normal bladder stroma, corroborated the evidence from
```

the clin. specimens and demonstrated that TN-C was strongly expressed around foci of stromal invasion. Thus, TN-C immunoreactivity may provide an addnl. tool in the assessment of early stromal invasion in bladder cancer.

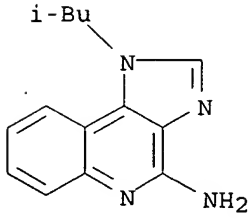
AN 2002:892826 CAPLUS <<LOGINID::20070309>>
DN 138:185087
TI Towards defining roles and relationships for tenascin-C and TGFβ-1 in the normal and neoplastic urinary bladder
AU Booth, Catherine; Harnden, Patricia; Selby, Peter J.; Southgate, Jennifer
CS Jack Birch Unit of Molecular Carcinogenesis, Department of Biology, University of York, York, YO10 5YW, UK
SO Journal of Pathology (2002), 198(3), 359-368
CODEN: JPTLAS; ISSN: 0022-3417
PB John Wiley & Sons Ltd.
DT Journal
LA English
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
     (FILE 'HOME' ENTERED AT 09:24:45 ON 09 MAR 2007)

     FILE 'REGISTRY' ENTERED AT 09:25:17 ON 09 MAR 2007
                EXP ISS-ODN/CN
L1             1 S IMIQUIMOD/CN
L2             1 S RESIQUIMOD/CN
L3             1 S MIZORIBINE/CN

     FILE 'CAPLUS' ENTERED AT 09:26:14 ON 09 MAR 2007
L4           223 S L3/THU
L5            17 S L4 AND CANCER
L6             5 S L5 NOT PY>2004
L7            16 S L2/THU AND CANCER
L8             0 S L7 NOT PY>2004
L9            25 S L2/THU AND INTERFERON
L10           17 S L9 NOT PY>2004
L11           66 S L1/THU AND INTERFERON
L12           34 S L11 NOT PY>2003
L13            3 S L12 AND CANCER

     INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
     AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
     CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
     DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 09:29:54 ON 09 MAR 2007
                SEA OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON
               ---------
               1    FILE BIOSIS
               2    FILE BIOTECHABS
               2    FILE BIOTECHDS
               2    FILE DDFU
               2    FILE DGENE
               2    FILE DRUGU
               1    FILE EMBASE
               1    FILE IFIPAT
               6    FILE MEDLINE
               1    FILE SCISEARCH
               1    FILE TOXCENTER
              37    FILE USPATFULL
               5    FILE USPAT2
               3    FILE WPIDS
               3    FILE WPINDEX
L14             QUE OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON
               ---------

     FILE 'MEDLINE' ENTERED AT 09:31:25 ON 09 MAR 2007
L15            6 S OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON
L16            0 S L15 AND IMIQUIMOD
L17            0 S IMIQUIMOD AND (ISS-ODN)
L18            0 S RESIQUIMOD AND (ISS-ODN)
L19            0 S BIFUNCTIONAL AND (ISS-ODN)

     FILE 'CAPLUS' ENTERED AT 09:33:06 ON 09 MAR 2007
L20            0 S BIFUNCTIONAL AND (ISS-ODN)
L21            4 S BIFUNCTIONAL AND (TOLL-LIKE)
L22        13469 S (INTERFERON(W)(ALPHA OR BETA))
L23         1140 S L22 AND CANCER
L24         9220 S L22 NOT PY>2002
L25          711 S L23 NOT PY>2002
L26           11 S L25 AND EXOGENOUS
L27        20039 S (INTERFERON(1A)(ALPHA OR BETA))
L28         1490 S L27 AND CANCER
L29          949 S L28 NOT PY>2002
L30           14 S L29 AND EXOGENOUS
```

L31 3 S L30 NOT L26

```
=> file registry
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 09:25:17 ON 09 MAR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:    7 MAR 2007  HIGHEST RN 925547-09-7
DICTIONARY FILE UPDATES:   7 MAR 2007  HIGHEST RN 925547-09-7

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> exp ISS-ODN/cn
E1            1     ISS 610/CN
E2            1     ISS 637/CN
E3            0 --> ISS-ODN/CN
E4            1     ISSAG3, TRANSPOSASE (STREPTOCOCCUS AGALACTIAE STRAIN A909)/C
                    N
E5            2     ISSAG4, TRANSPOSASE ORFA (STREPTOCOCCUS AGALACTIAE STRAIN A9
                    09)/CN
E6            2     ISSAG4, TRANSPOSASE ORFB (STREPTOCOCCUS AGALACTIAE STRAIN A9
                    09)/CN
E7            1     ISSAG5, TRANSPOSASE ORFA (STREPTOCOCCUS AGALACTIAE STRAIN A9
                    09)/CN
E8            1     ISSAG5, TRANSPOSASE ORFB (STREPTOCOCCUS AGALACTIAE STRAIN A9
                    09)/CN
E9            1     ISSAG6, TRANSPOSASE ORFA (STREPTOCOCCUS AGALACTIAE STRAIN A9
                    09)/CN
E10           1     ISSAG7, TRANSPOSASE ORFA (STREPTOCOCCUS AGALACTIAE STRAIN A9
                    09)/CN
E11           5     ISSAG8, TRANSPOSASE (STREPTOCOCCUS AGALACTIAE STRAIN A909)/C
                    N
E12           3     ISSAG9, TRANSPOSASE (STREPTOCOCCUS AGALACTIAE STRAIN A909)/C
                    N

=> s imiquimod/cn
L1            1 IMIQUIMOD/CN

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   99011-02-6  REGISTRY
ED   Entered STN:  09 Nov 1985
CN   1H-Imidazo[4,5-c]quinolin-4-amine, 1-(2-methylpropyl)- (9CI)  (CA INDEX
     NAME)
```

OTHER NAMES:
CN Aldara
CN Imiquimod
CN R 837
CN S 26308
MF C14 H16 N4
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
      (*File contains numerically searchable property data)
    Other Sources: WHO



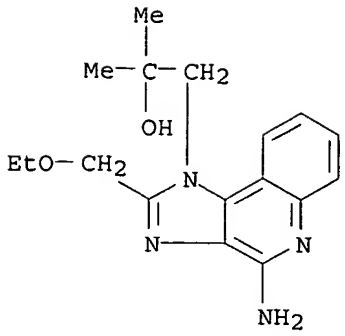
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

404 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
406 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s resiquimod/cn
L2 1 RESIQUIMOD/CN

=> d l2

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN 144875-48-9 REGISTRY
ED Entered STN: 11 Dec 1992
CN 1H-Imidazo[4,5-c]quinoline-1-ethanol, 4-amino-2-(ethoxymethyl)-α,α-dimethyl- (CA INDEX NAME)
OTHER NAMES:
CN 4-Amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol
CN R 848
CN Resiquimod
CN S 28463
DR 171742-32-8, 208711-44-8
MF C17 H22 N4 O2
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, BIOSIS, BIOTECHNO, CA, CAPLUS, CIN, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MRCK*, PHAR, PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
      (*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

164 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
164 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s mizoribine/cn
L3 1 MIZORIBINE/CN

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	19.65	19.86

FILE 'CAPLUS' ENTERED AT 09:26:14 ON 09 MAR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 9 Mar 2007 VOL 146 ISS 11
FILE LAST UPDATED: 7 Mar 2007 (20070307/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

http://www.cas.org/infopolicy.html

=> s l3/thu
417 L3
865164 THU/RL
L4 223 L3/THU
(L3 (L) THU/RL)

=> d l4 and cancer
'AND' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'
'CANCER' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'

The following are valid formats:

ABS --------- GI and AB
ALL --------- BIB, AB, IND, RE
APPS -------- AI, PRAI
BIB --------- AN, plus Bibliographic Data and PI table (default)
CAN --------- List of CA abstract numbers without answer numbers
CBIB -------- AN, plus Compressed Bibliographic Data
CLASS ------- IPC, NCL, ECLA, FTERM
DALL -------- ALL, delimited (end of each field identified)
DMAX -------- MAX, delimited for post-processing
FAM --------- AN, PI and PRAI in table, plus Patent Family data
FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers;
SCAN must be entered on the same line as the DISPLAY,
e.g., D SCAN or DISPLAY SCAN)
STD --------- BIB, CLASS

IABS -------- ABS, indented with text labels
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
ISTD -------- STD, indented with text labels

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

HIT --------- Fields containing hit terms
HITIND ------ IC, ICA, ICI, NCL, CC and index field (ST and IT)
containing hit terms
HITRN ------- HIT RN and its text modification
HITSTR ------ HIT RN, its text modification, its CA index name, and
its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

To display a particular field or fields, enter the display field codes. For a list of the display field codes, enter HELP DFIELDS at an arrow prompt (=>). Examples of formats include: TI; TI,AU; BIB,ST; TI,IND; TI,SO. You may specify the format fields in any order and the information will be displayed in the same order as the format specification.

All of the formats (except for SAM, SCAN, HIT, HITIND, HITRN, HITSTR, FHITSTR, HITSEQ, FHITSEQ, KWIC, and OCC) may be used with DISPLAY ACC to view a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):ti

L4 ANSWER 1 OF 223 CAPLUS COPYRIGHT 2007 ACS on STN

TI Pteridine derivatives as immunosuppressants, their preparation, pharmaceutical compositions, and use in therapy

=> s l4 and cancer
308330 CANCER
L5 17 L4 AND CANCER

=> s l5 not py>2004
2817580 PY>2004
L6 5 L5 NOT PY>2004

=> d l6 1-5 ti

L6 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
TI Inosine monophosphate dehydrogenase inhibitors and prodrugs in the treatment of cancer and immune disease

L6 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
TI Compositions comprising tumor-dendritic Fusion cells, recombinant human interleukin 12, antipyretic and immunosuppressant for cancer immunotherapy

L6 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
TI Method for determination of inosine 5'-monophosphate dehydrogenase activity in blood during immunosuppressant therapy

L6 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
TI Preparation of carbocyclic and heterocyclic fused-ring quinolinecarboxylic acid immunosuppressive agents

L6 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
TI Platinum-bredinin complex

=> d l6 1-5 ti abs bib

L6 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
TI Inosine monophosphate dehydrogenase inhibitors and prodrugs in the treatment of cancer and immune disease
AB The invention provides methods of treating cancer using inhibitors of inosine monophosphate dehydrogenase (IMPDH). The IMPDH inhibitors are combined with compds. that inhibit cellular processes regulated by GTP or ATP. Also provided are prodrugs of the IMPDH inhibitor mizoribine and its aglycon. The prodrugs are useful in practicing the methods of the invention, including immunosuppressive therapy and treatment of cancer by prolonged administration without addnl. therapeutic compds.
AN 2004:120731 CAPLUS <<LOGINID::20070309>>
DN 140:157496
TI Inosine monophosphate dehydrogenase inhibitors and prodrugs in the treatment of cancer and immune disease
IN Carson, Dennis A.; Leoni, Lorenzo M.; Cottam, Howard B.
PA The Regents of the University of California, USA
SO PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004012746	A2	20040212	WO 2003-US24325	20030801
	WO 2004012746	A3	20040805		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	AU 2003261354	A1	20040223	AU 2003-261354	20030801
	US 2004127435	A1	20040701	US 2003-632711	20030801
PRAI	US 2002-400583P	P	20020802		
	WO 2003-US24325	W	20030801		

OS MARPAT 140:157496

L6 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
TI Compositions comprising tumor-dendritic Fusion cells, recombinant human interleukin 12, antipyretic and immunosuppressant for cancer immunotherapy
AB The present invention relates to methods and compns. for treating and preventing cancer by administering a therapeutically ED of fusion cells formed by fusion of autologous dendritic cells and autologous non-dendritic cells, in combination with a cytokine or other mol. which stimulates or induces a cytotoxic T cell response and/or a humoral immune response.
AN 2004:119752 CAPLUS <<LOGINID::20070309>>
DN 140:162347
TI Compositions comprising tumor-dendritic Fusion cells, recombinant human interleukin 12, antipyretic and immunosuppressant for cancer immunotherapy
IN Ohno, Tsuneya
PA USA
SO U.S. Pat. Appl. Publ., 38 pp., Cont.-in-part of U.S. Ser. No. 12,134.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004028663	A1	20040212	US 2002-328998	20021224
	US 2002168351	A1	20021114	US 2001-12134	20011022
PRAI	US 2000-242154P	P	20001020		
	US 2001-12134	A2	20011022		

L6 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
TI Method for determination of inosine 5'-monophosphate dehydrogenase activity in blood during immunosuppressant therapy
AB The invention concerns the determination of IMP dehydrogenase(IMDPH) activity in
blood during cancer therapeutic IMDPH suppression treatment by using IMP substrate and NAD cofactor; and measuring spectrophotometrically one of the reaction components during formation of xanthosine 5'-monophosphate and NADH directly or after cleavage of the xanthosine 5'-monophosphate. Leukocytes are isolated from blood and resuspended in the plasma of the same patient; after sonication, substrate and cofactor are added; the mixture is incubated at 37°C, followed by centrifugation. Using HPLC separation, the quantity of xanthosine 5'-monophosphate is determined at 260 nm. Blood of cancer patients or patients undergoing organ transplantation are assayed by the method. Immunosuppressants used in the therapy are: mycophenolic acid, mycophenolate mofetil, tiazofurine, ribavirin, mizoribine, or VX-497. The invention also concerns a test kit for performing the IMDPH blood assay.
AN 1999:624652 CAPLUS <<LOGINID::20070309>>
DN 131:225481

TI Method for determination of inosine 5'-monophosphate dehydrogenase activity in blood during immunosuppressant therapy
IN Albrecht, Wolfgang; Bungers, Eva; Martin, Wolfgang; Guserle, Richard
PA Merckle G.m.b.H., Germany
SO Ger. Offen., 18 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19811313	A1	19990923	DE 1998-19811313	19980316
PRAI	DE 1998-19811313		19980316		

L6 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
TI Preparation of carbocyclic and heterocyclic fused-ring quinolinecarboxylic acid immunosuppressive agents
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I, II; R1, R2 = H, Cl, Br, CF3, alkyl; R3 = Ph, PhO, PhS (un)substituted PhNH, heterocyclyl, etc.; X = YCH2, CH2Y, CH2CH2Y, YCH2CH2, etc.; Y = (un)substituted CH2, O, S, (un)substituted NH; Z1-Z3 = N, (un)substituted CH] (e.g., I; R1 = 6-F, R2 = H, R3 = 4-MeC6H4, X = CH2CH2, Z1-Z3 = CH) [III; Q1, Q2 = S, (un)substituted NH, (un)substituted CH] (IV; Q3, Q4 = N, C; R11 = H, F, Cl, Br, CF3, alkyl), useful as immunosuppressants for the treatment of organ transplantation rejection, graft vs. host diseases, autoimmune diseases, cancer, chronic inflammatory diseases, etc., are prepared and I-, II-, III-, and IV-containing formulations presented.
AN 1995:846523 CAPLUS <<LOGINID::20070309>>
DN 123:256538
TI Preparation of carbocyclic and heterocyclic fused-ring quinolinecarboxylic acid immunosuppressive agents
IN Magolda, Ronald Louis; Pitts, William John; Jacobson, Irina Cipora; Behrens, Carl Henry; Orwat, Michael James; Batt, Douglas Guy
PA Du Pont Merck Pharmaceutical Co., USA
SO PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9506640	A1	19950309	WO 1994-US9463	19940826
	W: AU, BR, CA, CN, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5428040	A	19950627	US 1993-114712	19930831
	CA 2170349	A1	19950309	CA 1994-2170349	19940826
	AU 9476358	A	19950322	AU 1994-76358	19940826
	AU 690140	B2	19980423		
	EP 716652	A1	19960619	EP 1994-926555	19940826
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	HU 74585	A2	19970128	HU 1996-501	19940826
	JP 09501442	T	19970210	JP 1995-508162	19940826
	RU 2133740	C1	19990727	RU 1996-107400	19940826
	IL 110821	A	19970415	IL 1994-110821	19940830
	ZA 9406658	A	19960229	ZA 1994-6658	19940831
	US 5639759	A	19970617	US 1995-411251	19950327
	FI 9600933	A	19960228	FI 1996-933	19960228

```
     NO 9600811           A     19960429    NO 1996-811           19960228
     US 5874441           A     19990223    US 1997-820222        19970318
     US 6110910           A     20000829    US 1998-195366        19981118
PRAI US 1993-114712       A     19930831
     WO 1994-US9463       W     19940826
     US 1995-411251       A3    19950327
     US 1997-820222       A3    19970318
OS   MARPAT 123:256538

L6   ANSWER 5 OF 5  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Platinum-bredinin complex
AB   An aqueous mixture of 100 mg cis-dichlorodiammine platinum(II) and 110 mg AgNO3
     was stirred overnight at room temperature, filtered, 0.1 N HCl added to the
     filtrate, the mixture filtered, 850 mg bredinin added to the resulting
     diaquodiammine platinum(II) nitrate solution, and the whole stirred 1 wk at
     room temperature in the dark to give, after chromatog. over SiO2 gel, 150 mg
     Pt-bredinin complex.  An inhibitory ratio of the product was 20 μg
     Pt/mL against L5178Y cancer cells.
AN   1980:568561  CAPLUS <<LOGINID::20070309>>
DN   93:168561
TI   Platinum-bredinin complex
PA   Toyo Jozo Co., Ltd., Japan
SO   Jpn. Kokai Tokkyo Koho, 3 pp.
     CODEN: JKXXAF
DT   Patent
LA   Japanese
FAN.CNT 1
     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
PI   JP 55047696           A     19800404    JP 1978-120673          19780929
PRAI JP 1978-120673        A     19780929


=> s l2/thu and cancer
           164 L2
        865164 THU/RL
           119 L2/THU
                 (L2 (L) THU/RL)
        308330 CANCER
L7          16 L2/THU AND CANCER

=> s l7 not py>2004
       2817580 PY>2004
L8            0 L7 NOT PY>2004

=> s l2/thu and interferon
           164 L2
        865164 THU/RL
           119 L2/THU
                 (L2 (L) THU/RL)
         75697 INTERFERON
L9          25 L2/THU AND INTERFERON

=> s l9 not py>2004
       2817580 PY>2004
L10         17 L9 NOT PY>2004

=> d l10 1-17 ti

L10  ANSWER 1 OF 17  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Resiquimod, a new immune response modifier from the family of
     imidazoquinolinamines, inhibits allergen-induced Th2 responses, airway
     inflammation and airway hyper-reactivity in mice
```

L10 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Imiquimod and resiquimod in a mouse model: adjuvants for DNA vaccination by particle-mediated immunotherapeutic delivery

L10 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Resiquimod is a modest adjuvant for HIV-1 gag-based genetic immunization in a mouse model

L10 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Randomized, single-blind, placebo-controlled study of topical application of the immune response modulator resiquimod in healthy adults

L10 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI The novel synthetic immune response modifier R-848 (resiquimod) shifts human allergen-specific CD4+ TH2 lymphocytes into IFN-γ-producing cells

L10 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Inhibition of IgE production by the imidazoquinoline resiquimod in nonallergic and allergic donors

L10 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Dendritic cell maturation and IL-12 synthesis induced by the synthetic immune-response modifier S-28463

L10 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway

L10 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Imiquimod and resiquimod as novel immunomodulators

L10 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Clearance of infection with Mycobacterium bovis BCG in mice is enhanced by treatment with S28463 (R-848), and its efficiency depends on expression of wild-type Nramp1 (resistance allele)

L10 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: A pilot study

L10 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Current recommendations for the treatment of genital herpes

L10 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI S-28463: treatment of hepatitis C, interferon inducer

L10 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Gel formulations for topical drug delivery

L10 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Cytokine induction in hairless mouse and rat skin after topical application of the immune response modifiers imiquimod and S-28463

L10 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Effect of a novel topical immunomodulator, S-28463, on keratinocyte cytokine gene expression and production

L10 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI 1-Substituted, 2-substituted 1H-imidazo[4,5-c]quinolin-4-amines as antiviral and antitumor agents and inducers of biosynthesis of interferon

=> d l10 1 2 9 11 13 17 ti abs bib

L10 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Resiquimod, a new immune response modifier from the family of imidazoquinolinamines, inhibits allergen-induced Th2 responses, airway inflammation and airway hyper-reactivity in mice
AB Background: Allergen-induced sensitization and airway disease are the results of adverse immune reactions against environmental antigens that may be prevented or inhibited by immune modifying strategies. Objective: To investigate the effects of the novel immune response modifier resiquimod (R-848), from the family of imidazol-derivates, in a marine model of allergen-mediated Th2-immune responses and concomitant airway inflammation and airway hyper-reactivity. Methods: BALB/c mice were systemically sensitized with ovalbumin (OVA) on days 1 and 14 and challenged with OVA aerosol on days 28 and 29. R-848 was applied intranasally to sensitized animals once prior to the first allergen airway challenge, on day 27. Results: A single application of R-848 significantly reduced nos. of eosinophils and lymphocytes in bronchoalveolar lavage fluid and inhibited mucus gland hyperplasia, compared with sensitized and challenged controls. Associated with the decrease in airway inflammation, single intranasal treatment with R-848 abolished the development of airway hyper-reactivity after allergen sensitization and airway challenges. Addnl., Th2-cytokine production in lung tissues from sensitized and R-848-treated animals was reduced, whereas IL-12 and IFN-γ production was increased, compared with non-treated sensitized mice. Conclusions: These data indicate that R-848 effectively inhibits allergen-induced airway inflammation and hyper-reactivity by modulation of increased Th2-immune responses.
AN 2004:765477 CAPLUS <<LOGINID::20070309>>
DN 142:106842
TI Resiquimod, a new immune response modifier from the family of imidazoquinolinamines, inhibits allergen-induced Th2 responses, airway inflammation and airway hyper-reactivity in mice
AU Quarcoo, D.; Weixler, S.; Joachim, R. A.; Stock, P.; Kallinich, T.; Ahrens, B.; Hamelmann, E.
CS Department of Pediatric Pneumology and Immunology, Charite-Humboldt University, Berlin, Germany
SO Clinical and Experimental Allergy (2004), 34(8), 1314-1320
CODEN: CLEAEN; ISSN: 0954-7894
PB Blackwell Publishing Ltd.
DT Journal
LA English
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Imiquimod and resiquimod in a mouse model: adjuvants for DNA vaccination by particle-mediated immunotherapeutic delivery
AB Imiquimod, an immune response modifier and inducer of cytokines in vitro and in vivo, has been shown to have potent antiviral and antitumor activity and to act as an adjuvant for protein vaccination. We have undertaken studies in mice to investigate the potential of imiquimod and resiquimod to adjuvant DNA vaccination. These imidazoquinolines were administered by s.c. injection at the vaccination site immediately after particle-mediated immunotherapeutic delivery of plasmid DNA using a gene gun. Imiquimod was found to increase the number and maturation status of dendritic cells in draining lymph nodes, and to enhance antigen-specific CD4+ and CD8+ T cell responses, as assessed by analyses of clonal expansion, and the quantity and kinetics of cytokine production from these cells in lymph nodes and spleens collected after vaccination. A more substantial increase in IFN-γ-producing, compared with IL-4-producing CD4+ T cells suggested that imiquimod biased the immune response towards a predominance of Th1 cells. The analog resiquimod was found to be to produce a similar Th1 biased immune response with a 10-fold

reduced dose compared with imiquimod. Collectively, these studies suggest that both imiquimod and resiquimod may be suitable adjuvants for therapeutic DNA vaccines requiring induction of potent cytotoxic T cell responses.

AN 2004:285023 CAPLUS <<LOGINID::20070309>>
DN 141:138769
TI Imiquimod and resiquimod in a mouse model: adjuvants for DNA vaccination by particle-mediated immunotherapeutic delivery
AU Thomsen, Lindy L.; Topley, Peter; Daly, Maria G.; Brett, Sara J.; Tite, John P.
CS Department of Immunotherapeutics, GlaxoSmithKline Medicines Research Centre, Hertfordshire, SG1 2NY, UK
SO Vaccine (2004), 22(13-14), 1799-1809
CODEN: VACCDE; ISSN: 0264-410X
PB Elsevier Science Ltd.
DT Journal
LA English
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Imiquimod and resiquimod as novel immunomodulators
AB A review. Augmenting the host's natural immune response to viruses by the administration of exogenous cytokines such as interferon-α (IFN-α) is a strategy increasingly employed in antiviral therapeutics. Enhancing the release of endogenous cytokines is, however, an alternative approach. The imidazoquinolinamines imiquimod and resiquimod have demonstrated potency as inducers of IFN-α and other cytokines both in vitro and in vivo. Cytokine gene activation is mediated via the signal transducer and activator of transcription 1 (STAT-1) and involves the transcription factors NFκB and α4F1. Antiviral activity has been demonstrated against a variety of viruses, and clin. efficacy has been demonstrated against genital warts, herpes genitalis and molluscum contagiosum. Imiquimod is administered as a 5% cream (Aldara) and has been licensed for the treatment of anogenital warts in immunocompetent patients. Complete clearance of warts has been observed in up to half of treated patients with only local side effects reported. Resiquimod can be administered topically but also exists as an oral formulation. The range of potential infections for which these agents may have clin. utility includes chronic hepatitis C virus infection and Kaposi's sarcoma. In addition, the imidazoquinolinamines may find roles in the therapy of cancers and as vaccine adjuvants.
AN 2002:32301 CAPLUS <<LOGINID::20070309>>
DN 136:272485
TI Imiquimod and resiquimod as novel immunomodulators
AU Dockrell, D. H.; Kinghorn, G. R.
CS Department of Infectious Diseases, Royal Hallamshire Hospital, Sheffield, UK
SO Journal of Antimicrobial Chemotherapy (2001), 48(6), 751-755
CODEN: JACHDX; ISSN: 0305-7453
PB Oxford University Press
DT Journal; General Review
LA English
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

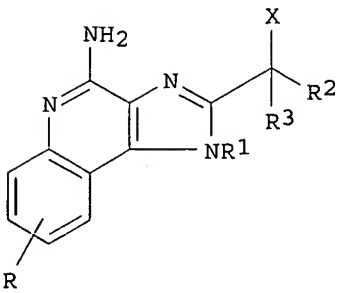
L10 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: A pilot study
AB Resiquimod (R-848), a topically active immune response modifier, induced production of interferon-α and interleukin-12 in cultured blood mononuclear cells and decreased genital herpes recurrences in an animal model. In this study, 52 patients with frequently recurrent genital herpes applied topical resiquimod gel 0.01% (twice or thrice

weekly) or 0.05% (once or twice weekly) or vehicle gel to herpes lesions for 3 wk. During the 6-mo observation period after treatment, median days to first recurrence in the pooled resiquimod group was 169 days, compared with 57 days for the vehicle group (P =.0058). In all, 32% of resiquimod-treated patients completed the observation period without a recurrence, compared with 6% of vehicle-treated patients (P =.039). Resiquimod 0.05% twice weekly produced dose-limiting inflammation at the lesion sites, but the other regimens were well tolerated. Application of resiquimod to genital herpes lesions appeared to reduce the frequency of recurrences.

AN 2001:561869 CAPLUS <<LOGINID::20070309>>
DN 135:313221
TI Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: A pilot study
AU Spruance, Spotswood L.; Tyring, Stephen K.; Smith, Michael H.; Meng, Tze-Chiang
CS Department of Medicine, School of Medicine, University of Utah, Salt Lake City, UT, 84132, USA
SO Journal of Infectious Diseases (2001), 184(2), 196-200
CODEN: JIDIAQ; ISSN: 0022-1899
PB University of Chicago Press
DT Journal
LA English
RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI S-28463: treatment of hepatitis C, interferon inducer
AB A review with 22 refs. on the synthesis, pharmacol., and clin. studies of S-28463, an interferon inducer with antiviral activity.
AN 1999:555369 CAPLUS <<LOGINID::20070309>>
DN 132:87525
TI S-28463: treatment of hepatitis C, interferon inducer
AU Graul, A.; Castaner, J.
CS Prous Science, Barcelona, 08080, Spain
SO Drugs of the Future (1999), 24(6), 622-627
CODEN: DRFUD4; ISSN: 0377-8282
PB Prous Science
DT Journal; General Review
LA English
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
TI 1-Substituted, 2-substituted 1H-imidazo[4,5-c]quinolin-4-amines as antiviral and antitumor agents and inducers of biosynthesis of interferon
GI



I

AB 1-Substituted, 2-substituted 1H-imidazo[4,5-c]-quinolin-4-amines I [wherein R1 is selected from the group consisting of: hydroxyalkyl of one to about six carbon atoms and alkoxyalkyl wherein the alkoxy moiety is of one to about four carbon atoms and the alkyl moiety is of one to about six carbon atoms; R2 and R3 are independently selected from the group consisting of hydrogen and alkyl of one to about four carbon atoms; X is selected from the group consisting of alkoxy of one to about four carbon atoms, alkoxyalkyl wherein the alkoxy moiety is of one to about four carbon atoms and the alkyl moiety is of one to about four carbon atoms, hydroxyalkyl of one to about four carbon atoms, and hydroxy; and R is selected from the group consisting of hydrogen, straight chain or branched chain alkoxy of one to about four carbon atoms, halogen, and straight chain or branched chain alkyl of one to about four carbon atoms; or a pharmaceutically acceptable acid addition salt thereof] are disclosed. These compds. function as antiviral agents, they induce biosynthesis of interferon, and they inhibit tumor formation in animal models. This invention also provides intermediates for preparing such compds., pharmaceutical compns. containing such compds., and pharmacol. methods of using such compds. I inhibited Herpes simplex virus type II lesions in guinea pigs and were also active against vesicular stomatitis virus in vitro. Interferon-α induction in human cells by I: at dose concentration of, e.g., 0.50 μg/mL, α reference units/mL of up to 2500 were observed Inhibition of MC-26 tumors in mice by I: at dose of 30 mg/kg, number of colonies as low as 123 ± 31 vs. 385 ± 31 for control were observed

AN 1995:420800 CAPLUS <<LOGINID::20070309>>
DN 123:83363
TI 1-Substituted, 2-substituted 1H-imidazo[4,5-c]quinolin-4-amines as antiviral and antitumor agents and inducers of biosynthesis of interferon
IN Gerster, John F.; Crooks, Stephen L.; Lindstrom, Kyle J.
PA Minnesota Mining and Manufacturing Co., USA
SO U.S., 26 pp. Cont.-in-part of U.S. Ser. No. 838,475, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5389640	A	19950214	US 1992-938295	19920828
	CA 2104782	A1	19920902	CA 1992-2104782	19920220
	CA 2104782	C	20010807		
	EP 872478	A2	19981021	EP 1998-105754	19920220
	EP 872478	A3	19981104		
	EP 872478	B1	20021218		
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE				
	CA 2289219	C	20030520	CA 1992-2289219	19920220
	ZA 9201540	A	19921125	ZA 1992-1540	19920228
	IL 114570	A	19961031	IL 1992-114570	19920301
	US 5605899	A	19970225	US 1994-353802	19941212
	US 5741909	A	19980421	US 1997-789264	19970128
	US 5977366	A	19991102	US 1998-60010	19980414
	US 6348462	B1	20020219	US 1999-386486	19990827
	US 2002115861	A1	20020822	US 2001-974038	20011009
	US 6465654	B2	20021015		
	US 2003119861	A1	20030626	US 2002-238661	20020910
	US 6608201	B2	20030819		
	US 2003212270	A1	20031113	US 2003-436905	20030513
	US 6686472	B2	20040203		
	US 2004122231	A1	20040624	US 2003-731826	20031209
	US 6790961	B2	20040914		
PRAI	US 1991-662926	B2	19910301		
	US 1991-687326	B2	19910418		

```
     US 1992-838475        B2     19920219
     CA 1992-2104782       A3     19920220
     EP 1992-906763        A3     19920220
     IL 1992-101110        A3     19920301
     US 1992-938295        A3     19920828
     US 1994-353802        A3     19941212
     US 1997-789264        A3     19970128
     US 1998-60010         A3     19980414
     US 1999-386486        A1     19990827
     US 2001-974038        A3     20011009
     US 2002-238661        A3     20020910
     US 2003-436905        A3     20030513
OS   MARPAT 123:83363


=> s l1/thu and interferon
          406 L1
       865164 THU/RL
          337 L1/THU
                (L1 (L) THU/RL)
        75697 INTERFERON
L11        66 L1/THU AND INTERFERON

=> s l11 not py>2003
      3948023 PY>2003
L12        34 L11 NOT PY>2003

=> s L12 and cancer
       308330 CANCER
L13         3 L12 AND CANCER

=> d L13 1-3 ti

L13  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   The use of toll-like receptor-7 agonist in the treatment of basal cell
     carcinoma: an overview

L13  ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Imiquimod 5% cream (Aldara)

L13  ANSWER 3 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   A phase I clinical trial of imiquimod, an oral interferon
     inducer, administered daily


=> d L13 1-3 ti abs bib

L13  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   The use of toll-like receptor-7 agonist in the treatment of basal cell
     carcinoma: an overview
AB   A review.  Basal cell carcinoma (BCC) is a subtype of nonmelanoma skin
     cancer (NMSC), with an increasing incidence worldwide.  Currently,
     excision of the tumor with histol. control is the standard therapy.  However,
     high incidence rates have led to concern about the economic burden imposed
     by BCC management in many countries.  Imiquimod is a member of a novel
     class of immune response modifiers (IRM), which works by using the
     toll-like receptor (TLR)-7.  Although the exact mode of action is so far
     unknown, it is suggested to induce the expression of different cytokines
     like interleukin (IL)-1, IL-6, IL-12, interferon (IFN)-α
     and tumor necrosis factor (TNF)-α, which stimulate or enhance both
     the innate immune system and the cell-mediated immune response.  Preclin.
     studies have indicated the potential of this TLR-7 agonist for the
     treatment of precancers and tumors in humans.  A number of Phase II trials
     have demonstrated the efficacy of imiquimod for the treatment of BCC,
```

although the most appropriate dosing regimen is being confirmed in Phase III studies. Imiquimod 5% cream for the treatment of mainly superficial BCC appears to be an effective and well-tolerated treatment option.

AN 2004:63952 CAPLUS <<LOGINID::20070309>>
DN 140:121944
TI The use of toll-like receptor-7 agonist in the treatment of basal cell carcinoma: an overview
AU Stockfleth, E.; Trefzer, U.; Garcia-Bartels, C.; Wegner, T.; Schmook, T.; Sterry, W.
CS Department of Dermatology, University Hospital Charite, Berlin, D-10117, Germany
SO British Journal of Dermatology, Supplement (2003), 149(66), 53-56
CODEN: BJDSA9; ISSN: 0366-077X
PB Blackwell Publishing Ltd.
DT Journal; General Review
LA English
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
TI Imiquimod 5% cream (Aldara)
AB A review with 23 refs. Imiquimod is a novel synthetic mol. with potent immune-modifying activities. Formulated in a 5% vanishing cream as Aldara, this self-applied therapy has shown good efficacy and safety in the treatment of external genital and perianal warts caused by human papillomavirus (HPV) infection (Condyloma acuminata). The mol. does not demonstrate direct antiviral activity, but through induction of cytokines results in immune-based resolution of wart tissue and reduction of viral burden.

Phase III trials of imiquimod have demonstrated that patients who experience complete clearance of either new or recalcitrant warts tend to remain clear, possibly related to Th1 immune recognition and memory. Self-application, good tolerability and a unique mechanism of action combine to make imiquimod a reasonable first-line therapy for genital warts. The effects of imiquimod on immune function suggest several potential uses. Preclin. studies of infection with herpes simplex virus (HSV), cutaneous leishmaniasis, Rift Valley Fever virus and vesiculostomatitis virus have shown reduced viral persistence, reduced recurrence (HSV) and diminished pathol. (Leishmania donovani). In a murine tumor model using the FCB bladder cancer cell line, imiquimod behaves as a potent adjuvant leading to immune-based tumor cell eradication and immunity against subsequent FCB cell challenge. The ability of imiquimod to induce significant production of interferon alpha (IFN-α) by monocytes/macrophages suggests that diseases responsive to recombinant interferon therapy, such as basal cell carcinoma, may be reasonable clin. targets. The induction of tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ) and interleukin-12 (IL-12) leads to inhibition of IL-5, with animal models demonstrating immune deviation away from Th2 immune responses. The observation that several patients with hepatitis C infection and eosinophilia showed normalization of elevated eosinophil counts in association with oral imiquimod therapy encourages further exploration of the immune modifying properties of this novel mol. This review is focused on the use of imiquimod for the treatment of external genital and perianal warts.

AN 1998:198531 CAPLUS <<LOGINID::20070309>>
DN 128:316756
TI Imiquimod 5% cream (Aldara)
AU Slade, H. B.; Owens, M. L.; Tomai, M. A.; Miller, R. L.
CS 3M Pharmaceuticals, St Paul, MN, 55144-1000, USA
SO Expert Opinion on Investigational Drugs (1998), 7(3), 437-449
CODEN: EOIDER; ISSN: 1354-3784
PB Ashley Publications
DT Journal; General Review

LA English
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
TI A phase I clinical trial of imiquimod, an oral interferon inducer, administered daily
AB Imiquimod is an orally active interferon inducer with anti-tumor activity in exptl. animals. In this study the tolerability, toxicity and biol. effects of daily oral imiquimod administration were investigated in 21 patients with refractory cancer. Patients were treated with doses of 25 mg, 50 mg, 100 mg or 200 mg on a projected 112 day course. Only three patients completed the course, all at the 50 mg dose. Treatment toxicities were dose related and mainly comprised flu-like symptoms, nausea and lymphopenia. Of the 21 patients, five received dose redns. and in five treatment was discontinued because of treatment-related toxicity. The biol. activity of imiquimod was confirmed by significant and sustained rises in peripheral blood mononuclear cell (PBMC) 2-5A synthetase (2-5AS) levels at all doses. At 100 mg and 200 mg these occurred within the first 24 h of administration. Levels of neopterin and β2-microglobulin (β2M) were also significantly elevated when assessed after three weeks' treatment. Interferon production was not demonstrated within the first 24 h of the initial dose but, following repeated doses, ten of the patients developed detectable serum interferon concns. with a maximum value of 5600 IU mL-1 recorded. Administration of imiquimod did not have any significant effect on serum levels of tumor necrosis factor (TNF) or interleukin 1 (IL-1), nor did it lead to development of detectable levels of antibodies to interferon. One mixed clin. response was observed after 4 wk' treatment at 100 mg in a patient with renal cell cancer. Daily administration of imiquimod causes activation of the interferon production system but at higher doses results in unacceptable toxicity. Further investigation of imiquimod as an interferon-inducing agent in cancer patients is suggested at either the lower dose levels or employing alternative dosing schedules.
AN 1996:707118 CAPLUS <<LOGINID::20070309>>
DN 126:14415
TI A phase I clinical trial of imiquimod, an oral interferon inducer, administered daily
AU Savage, P.; Horton, V.; Moore, J.; Owens, M.; Witt, P.; Gore, M. E.
CS Department Medicine, Royal Marsden Hospital, London, SW6 6JJ, UK
SO British Journal of Cancer (1996), 74(9), 1482-1486
CODEN: BJCAAI; ISSN: 0007-0920
PB Stockton
DT Journal
LA English

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	77.41	97.27

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-10.92	-10.92

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE, AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 09:29:54 ON 09 MAR 2007

68 FILES IN THE FILE LIST IN STNINDEX

```
Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s oligonucleotide and (ISS-ODN) and interferon
           1   FILE BIOSIS
           2   FILE BIOTECHABS
           2   FILE BIOTECHDS
           2   FILE DDFU
           2   FILE DGENE
           2   FILE DRUGU
           1   FILE EMBASE
  29 FILES SEARCHED...
           1   FILE IFIPAT
           6   FILE MEDLINE
           1   FILE SCISEARCH
           1   FILE TOXCENTER
          37   FILE USPATFULL
           5   FILE USPAT2
  64 FILES SEARCHED...
           3   FILE WPIDS
           3   FILE WPINDEX

  15 FILES HAVE ONE OR MORE ANSWERS,   68 FILES SEARCHED IN STNINDEX

L14  QUE OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON

=> file medline
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                   1.89      99.16

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
                                                     ENTRY    SESSION
CA SUBSCRIBER PRICE                                   0.00     -10.92

FILE 'MEDLINE' ENTERED AT 09:31:25 ON 09 MAR 2007

 FILE LAST UPDATED: 8 Mar 2007 (20070308/UP).  FILE COVERS 1950 TO DATE.

  All regular MEDLINE updates from November 15 to December 16 have been
  added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R))
  and 2007 tree numbers.

  The annual reload will be available in early 2007.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

=> s oligonucleotide and (ISS-ODN) and interferon
         57990 OLIGONUCLEOTIDE
          2702 ISS
          2685 ODN
            38 ISS-ODN
                 (ISS(W)ODN)
         97513 INTERFERON
L15          6 OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON

=> d l15 1-6 ti

L15  ANSWER 1 OF 6     MEDLINE on STN
TI   Suppression of allergic response by CpG motif oligodeoxynucleotide-house-
     dust mite conjugate in animal model of allergic rhinitis.
```

L15 ANSWER 2 OF 6 MEDLINE on STN
TI Dendritic cells and HIV infection: activating dendritic cells to boost immunity.

L15 ANSWER 3 OF 6 MEDLINE on STN
TI CpG-C ISS-ODN activation of blood-derived B cells from healthy and chronic immunodeficiency virus-infected macaques.

L15 ANSWER 4 OF 6 MEDLINE on STN
TI Molecular and cellular mechanisms of protective immunity to coccidioidomycosis.

L15 ANSWER 5 OF 6 MEDLINE on STN
TI CpG-C immunostimulatory oligodeoxyribonucleotide activation of plasmacytoid dendritic cells in rhesus macaques to augment the activation of IFN-gamma-secreting simian immunodeficiency virus-specific T cells.

L15 ANSWER 6 OF 6 MEDLINE on STN
TI A minimal human immunostimulatory CpG motif that potently induces IFN-gamma and IFN-alpha production.

=> d l15 1-6 ti abs bib

L15 ANSWER 1 OF 6 MEDLINE on STN
TI Suppression of allergic response by CpG motif oligodeoxynucleotide-house-dust mite conjugate in animal model of allergic rhinitis.
AB BACKGROUND: Although there have been many therapeutic options for allergic disease, the true allergen desensitization remains a challenging goal. The classic immunotherapy has a limited efficacy, is inconvenient, and has a risk of anaphylaxis. Recent reports revealed that immunostimulatory DNA sequences (ISS-oligdeoxynucleotide [ODN], CpG motif) act as a strong Th1 response-inducing adjuvants and that DNA-based vaccination might be an effective therapeutic option. In this study, we investigate whether ISS-ODN/Dermatophagoides farinae (Der f) conjugate has antiallergic effects in the allergic rhinitis mouse model, sensitive to house-dust mites. Der f is the most common allergen-inducing allergic rhinitis in Korea. METHODS: C57BL/6 mice were sensitized with crude extract of Der f. After injection of ISS-ODN or ISS-ODN/Der f conjugate, several parameters of allergic response were evaluated. RESULTS: Scratching and sneezing symptoms and eosinophilic infiltration into nasal mucosa were suppressed by injection with ISS-ODN only and ISS-ODN/Der f conjugate. Interleukin-5 level was decreased and interferon gamma level was increased in nasal lavage fluid by injection of ISS-ODN/Der f conjugate. Der f-specific immunoglobulin E was decreased by injection of ISS-ODN or Der f / ISS-ODN conjugate; however, these were not statistically significant. Transforming growth factor beta1 secreted by cultured splenocyte was increased significantly in ISS-ODN/Der f conjugate group. CONCLUSION: These results suggest ISS-ODN/Der f conjugate induces an antiallergic effect and induces an increase in transforming growth factor beta1 level in the allergic rhinitis model using Der f allergen. Allergic response developed by Der f allergen could be more effectively reduced by injection with ISS-ODN/Der f conjugate than by injection with ISS-ODN only.
AN 2006262068 MEDLINE <<LOGINID::20070309>>
DN PubMed ID: 16686392
TI Suppression of allergic response by CpG motif oligodeoxynucleotide-house-dust mite conjugate in animal model of allergic rhinitis.
AU Mo Ji-Hun; Park Seok-Won; Rhee Chae-Seo; Takabayashi Kenji; Lee Seung Sin; Quan Song-Hua; Kim In-Sang; Min Il Yang-Gi; Raz Eyal; Lee Chul Hee
CS Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National

University College of Medicine, Seoul, Korea.
SO American journal of rhinology, (2006 Mar-Apr) Vol. 20, No. 2, pp. 212-8.
Journal code: 8807268. ISSN: 1050-6586.
CY United States
DT (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 200611
ED Entered STN: 12 May 2006
Last Updated on STN: 19 Dec 2006
Entered Medline: 29 Nov 2006

L15 ANSWER 2 OF 6 MEDLINE on STN
TI Dendritic cells and HIV infection: activating dendritic cells to boost immunity.
AB Dendritic cells (DCs) are white blood cells that coordinate innate and adaptive immunity. They are distributed within epithelia and mucosal-associated lymphoid tissues, positioned to entrap incoming pathogens or vaccines. Human immunodeficiency virus (HIV) and the non-human primate equivalent (SIV) exploit DCs to amplify infection, underscoring the need to harness strategies that promote presentation of virus by DCs to stimulate potent anti-viral immunity instead of virus transmission. Two main subsets of DCs need to be considered: myeloid (MDC) and plasmacytoid (PDC) subsets. Using the SIV-macaque system to advance oral vaccine research, we examined macaque PDC and MDC biology, identifying ways to activate DCs and boost antiviral immunity. Immunostimulatory oligodeoxyribonucleotides (ISS-ODNs) stimulated PDC/MDC mixtures to up-regulate co-stimulatory molecule expression and to secrete both IFN-alpha and IL-12. Additionally, ISS-ODNs augmented SIV-specific IFN-gamma responses induced by virus-bearing DCs. ISS-ODN-driven DC activation is being pursued to improve oral/nasopharyngeal mucosal vaccines and therapies against HIV.
AN 2006247894 MEDLINE <<LOGINID::20070309>>
DN PubMed ID: 16672547
TI Dendritic cells and HIV infection: activating dendritic cells to boost immunity.
AU Teleshova N; Kenney J; Robbiani M
CS Center for Biomedical Research, Population Council, 1230 York Avenue, New York, NY 10021, USA.
NC DE015512 (NIDCR)
DE016256 (NIDCR)
DE016534 (NIDCR)
HD041752 (NICHD)
P01S AI052048 (NIAID)
R01S AI040877 (NIAID)
R21S AI060405 (NIAID)
RR00164 (NCRR)
U19 AI065413 (NIAID)
SO Advances in dental research, (2006) Vol. 19, No. 1, pp. 36-41. Electronic Publication: 2006-04-01.
Journal code: 8802131. E-ISSN: 1544-0737.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LA English
FS Dental Journals
EM 200607
ED Entered STN: 5 May 2006
Last Updated on STN: 19 Jul 2006
Entered Medline: 18 Jul 2006

L15 ANSWER 3 OF 6 MEDLINE on STN
TI CpG-C ISS-ODN activation of blood-derived B cells from healthy and chronic immunodeficiency virus-infected macaques.
AB Cytosine-phosphate-guanine class C (CpG-C) immunostimulatory sequence oligodeoxynucleotides (ISS-ODNs) activate human B cells and dendritic cells (DCs), properties that suggest potential use as a novel adjuvant to enhance vaccine efficacy. After demonstrating that the CpG-C ISS -ODN C274 activates macaque DCs, we examined in vitro activation of macaque B cells by C274 as a prelude to evaluation of this molecule as an adjuvant in the testing of candidate human immunodeficiency virus vaccines in the rhesus macaque-simian immunodeficiency virus (SIV) model. C274 induced macaque CD20(+) B cells to proliferate more strongly than CD40 ligand or CpG-B ISS-ODN. C274 enhanced B cell survival; increased viability was most evident after 3-7 days of culture. Increased expression of CD40, CD80, and CD86 by B cells was apparent within 24 h of exposure to C274 and persisted for up to 1 week. C274-stimulated, B cell-enriched and peripheral blood mononuclear cell suspensions from naive and immunodeficiency virus-infected monkeys secreted several cytokines [e.g., interleukin (IL)-3, IL-6, IL-12, interferon-alpha] and chemokines [e.g., monocyte chemoattractant protein-1/CC chemokine ligand 2 (CCL2), macrophage-inflammatory protein-1alpha/CCL3, IL-8/CXC chemokine ligand 8]. In comparison, exposure of macaque B cells to SIV had minimal impact on surface phenotype, despite inducing cytokine and chemokine production in cells from infected and uninfected animals. These observations emphasize the need to identify strategies to optimally boost immune function, as immunodeficiency viruses themselves only partially activate B cells and DCs. The ability of C274 to stimulate B cells and DCs in healthy and infected monkeys suggests its possible use as a broad-acting adjuvant to be applied in the rhesus macaque model for the development of preventative and therapeutic vaccines.
AN 2006059047 MEDLINE <<LOGINID::20070309>>
DN PubMed ID: 16443827
TI CpG-C ISS-ODN activation of blood-derived B cells from healthy and chronic immunodeficiency virus-infected macaques.
AU Teleshova N; Kenney J; Williams V; Van Nest G; Marshall J; Lifson J D; Sivin I; Dufour J; Bohm R; Gettie A; Pope M
CS Population Council, 1230 York Avenue, New York, NY 10021, USA.
NC DE016256 (NIDCR)
N01-CO-12400 (NCI)
R01 AI040877 (NIAID)
R21 AI060405 (NIAID)
RR00164 (NCRR)
SO Journal of leukocyte biology, (2006 Feb) Vol. 79, No. 2, pp. 257-67.
Journal code: 8405628. ISSN: 0741-5400.
CY United States
DT (COMPARATIVE STUDY)
(IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LA English
FS Priority Journals
EM 200605
ED Entered STN: 31 Jan 2006
Last Updated on STN: 12 May 2006
Entered Medline: 11 May 2006

L15 ANSWER 4 OF 6 MEDLINE on STN
TI Molecular and cellular mechanisms of protective immunity to coccidioidomycosis.
AB Coccidioides immitis is endemic in the soil of the desert Southwest. It causes a respiratory infection that is usually mild, but can last months and may disseminate beyond the lung. Disseminated infections can be fatal

or require life-long therapy. Development of an effective vaccine may be a successful method of preventing serious disease. In this paper, we show that immunostimulatory-oligodeoxynucleotides (ISS-ODN) are an effective adjuvant for a recombinant coccidioidal protein known as antigen 2/proline rich antigen. Protective immunity induced by this ISS-ODN-based vaccine requires IL-12, interferon -gamma and MHC Class II-restricted T-cells. Cytotoxic CD8 T-cells are not required. This study elucidates the mechanisms needed to elicit successful immunity against coccidioidomycosis, and holds promise for development of an effective coccidioidal vaccine against coccidioidomycosis.

AN 2005697159 MEDLINE <<LOGINID::20070309>>
DN PubMed ID: 16181709
TI Molecular and cellular mechanisms of protective immunity to coccidioidomycosis.
AU Kirkland Theo N; Raz Eyal; Datta Sandip K
CS The Department of Pathology and Medicine, University of California-San Diego School of Medicine, 9500 Gilman Drive, La Jolla, CA 92093, USA.. tkirkland@ucsd.edu
NC R01 GM 066119 (NIGMS)
R37 AI 19149 (NIAID)
SO Vaccine, (2006 Jan 23) Vol. 24, No. 4, pp. 495-500. Electronic Publication: 2005-08-15.
Journal code: 8406899. ISSN: 0264-410X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 200604
ED Entered STN: 31 Dec 2005
Last Updated on STN: 26 Apr 2006
Entered Medline: 25 Apr 2006

L15 ANSWER 5 OF 6 MEDLINE on STN
TI CpG-C immunostimulatory oligodeoxyribonucleotide activation of plasmacytoid dendritic cells in rhesus macaques to augment the activation of IFN-gamma-secreting simian immunodeficiency virus-specific T cells.
AB There are two principle subsets of dendritic cells (DCs); CD11c(+)CD123(-) myeloid DCs (MDCs) and CD11c(-)CD123(+) plasmacytoid DCs (PDCs). DC activation via TNF-TNFRs (e.g., CD40L) and TLRs (e.g., immunostimulatory oligodeoxyribonucleotides (ISS-ODNs)) is crucial for maximal stimulation of innate and adaptive immunity. Macaque DC biology is being studied to improve HIV vaccines using the SIV macaque model. Using lineage (Lin) markers to exclude non-DCs, Lin(-)HLA-DR(+)CD11c(+)CD123(-) MDCs and Lin(-)HLA-DR(+)CD11c(-)CD123(+) PDCs were identified in the blood of uninfected macaques and healthy macaques infected with SIV or simian-human immunodeficiency virus. Overnight culture of DC-enriched Lin-depleted cells increased CD80 and CD86 expression. IL-12 production and CD80/CD86 expression by MDC/PDC mixtures was further enhanced by CD40L and ISS-ODN treatment. A CpG-B ISS-ODN increased CD80/CD86 expression by PDCs, but resulted in little IFN-alpha secretion unless IL-3 was added. In contrast, a CpG-C ISS-ODN and aldrithiol-2-inactivated (AT-2) SIV induced considerable PDC activation and IFN-alpha release without needing exogenous IL-3. The CpG-C ISS-ODN also stimulated IL-12 release (unlike AT-2 SIV) and augmented DC immunostimulatory activity, increasing SIV-specific T cell IFN-gamma production induced by AT-2 SIV-presenting MDC/PDC-enriched mixtures. These data highlight the functional capacities of MDCs and PDCs in naive as well as healthy, infected macaques, revealing a promising CpG-C ISS-ODN-driven DC activation strategy that boosts immune function to augment preventative and therapeutic vaccine efficacy.

AN 2004369784 MEDLINE <<LOGINID::20070309>>
DN PubMed ID: 15265893
TI CpG-C immunostimulatory oligodeoxyribonucleotide activation of plasmacytoid dendritic cells in rhesus macaques to augment the activation of IFN-gamma-secreting simian immunodeficiency virus-specific T cells.
AU Teleshova Natalia; Kenney Jessica; Jones Jennifer; Marshall Jason; Van Nest Gary; Dufour Jason; Bohm Rudolf; Lifson Jeffrey D; Gettie Agegnehu; Pope Melissa
CS Center for Biomedical Research, Population Council, New York, NY 10021, USA.
NC R01 AI40877 (NIAID)
R21 AI52060 (NIAID)
RR00164 (NCRR)
SO Journal of immunology (Baltimore, Md. : 1950), (2004 Aug 1) Vol. 173, No. 3, pp. 1647-57.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200411
ED Entered STN: 28 Jul 2004
Last Updated on STN: 3 Nov 2004
Entered Medline: 2 Nov 2004

L15 ANSWER 6 OF 6 MEDLINE on STN
TI A minimal human immunostimulatory CpG motif that potently induces IFN-gamma and IFN-alpha production.
AB Recent reports have shown that immunostimulatory sequences (ISS) containing CpG motifs have minimal length requirements (>/=12 bases) for the exertion of immune-enhancing function upon mammalian cells. Herein we demonstrate that short ISS (5-7 bases), which exhibit no activity on their own, induce IFN-gamma and IFN-alpha secretion from human peripheral blood mononuclear cells when adsorbed to the surface of cationic poly(D,L-lactide-co-glycolide) microparticles (cPLGA). Utilizing this technique, we discovered a minimal ISS sequence for induction of IFN-gamma and IFN-alpha from human cells: 5'-TCGXX-3'. These short ISS/cPLGA formulations targeted PDC in similar fashion to longer ISS ODN, the activity of which does not require (but is enhanced by) cPLGA. PDC stimulated with short ISS/cPLGA responded with enhanced uptake of ISS and elevated production of cytokines, including IFN-alpha. However, ISS-responsive B cells did not respond to short ISS/cPLGA, underlining the plasmacytoid dendritic cell selectivity of this formulation. These results describe a novel technique for formulating active, but very short, ISS oligodeoxynucleotide that allows for the dissection and characterization of minimal immunostimulatory CpG motifs.
AN 2003350780 MEDLINE <<LOGINID::20070309>>
DN PubMed ID: 12884285
TI A minimal human immunostimulatory CpG motif that potently induces IFN-gamma and IFN-alpha production.
AU Fearon Karen; Marshall Jason D; Abbate Christi; Subramanian Sandhya; Yee Priscilla; Gregorio Josh; Teshima Glen; Ott Gary; Tuck Stephen; Van Nest Gary; Coffman Robert L
CS Dynavax Technologies Corporation, Berkeley, CA 94710, USA.
SO European journal of immunology, (2003 Aug) Vol. 33, No. 8, pp. 2114-22.
Journal code: 1273201. ISSN: 0014-2980.
CY Germany: Germany, Federal Republic of
DT (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

```
EM   200309
ED   Entered STN: 29 Jul 2003
     Last Updated on STN: 30 Sep 2003
     Entered Medline: 29 Sep 2003


=> s l15 and imiquimod
           822 IMIQUIMOD
L16          0 L15 AND IMIQUIMOD

=> s imiquimod and (ISS-ODN)
           822 IMIQUIMOD
          2702 ISS
          2685 ODN
            38 ISS-ODN
                 (ISS(W)ODN)
L17          0 IMIQUIMOD AND (ISS-ODN)

=> s resiquimod and (ISS-ODN)
            46 RESIQUIMOD
          2702 ISS
          2685 ODN
            38 ISS-ODN
                 (ISS(W)ODN)
L18          0 RESIQUIMOD AND (ISS-ODN)

=> s bifunctional and (ISS-ODN)
          6994 BIFUNCTIONAL
          2702 ISS
          2685 ODN
            38 ISS-ODN
                 (ISS(W)ODN)
L19          0 BIFUNCTIONAL AND (ISS-ODN)

=> file caplus
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                   2.49     101.65

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
                                                     ENTRY    SESSION
CA SUBSCRIBER PRICE                                   0.00     -10.92

FILE 'CAPLUS' ENTERED AT 09:33:06 ON 09 MAR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 9 Mar 2007  VOL 146 ISS 11
FILE LAST UPDATED: 7 Mar 2007  (20070307/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:
```

http://www.cas.org/infopolicy.html

```
=> s bifunctional and (ISS-ODN)
         20852 BIFUNCTIONAL
          2486 ISS
          3353 ODN
            52 ISS-ODN
                 (ISS(W)ODN)
L20          0 BIFUNCTIONAL AND (ISS-ODN)

=> s bifunctional and (Toll-like)
         20852 BIFUNCTIONAL
          8154 TOLL
        779044 LIKE
          7141 TOLL-LIKE
                 (TOLL(W)LIKE)
L21          4 BIFUNCTIONAL AND (TOLL-LIKE)

=> d l21 1-4 ti

L21  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Polynucleotide marker genes and their expression for diagnosis of
     endotoxemia-related conditions in horses

L21  ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Design of bifunctional siRNAs: Combining immunostimulation and
     gene-silencing in one single siRNA molecule

L21  ANSWER 3 OF 4  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   MyD88-dependent and -independent signaling by IL-1 in neurons probed by
     bifunctional Toll/IL-1 receptor domain/BB-loop mimetics

L21  ANSWER 4 OF 4  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Gene expression profiles in the diagnosis and treatment of Alzheimer's
     disease


=> d l21 1-4 ti abs bib

L21  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Polynucleotide marker genes and their expression for diagnosis of
     endotoxemia-related conditions in horses
AB   The invention discloses isolated endotoxemia marker polynucleotides
     selected from any one of 163 different polynucleotide sequences, or
     variants thereof.  Endotoxemia (also called septic shock or septic
     syndrome)-related conditions are diagnosed in a test subject by aberrant
     expression of at least one of the endotoxemia markers or variants thereof.
     Of practical use is the early diagnosis of disease, determining those animals
at
     risk of developing endotoxemia, monitoring of an animal's immune response
     to the disease, and the enablement of better treatments.  The
     differentially expressed markers were identified by GeneChip anal. using
     Affymetrix technol. of blood obtained from normal horses and from horses
     with clin. evidence of an endotoxemia-related condition.  A gene signature
     of 159 genes demonstrates a specificity of 99% for toxemia in a population
     sample size of over 850 individuals.  Of particular interest is the
     diagnosis of laminitis in hoofed animals, including horses.
AN   2007:61320  CAPLUS <<LOGINID::20070309>>
DN   146:182524
TI   Polynucleotide marker genes and their expression for diagnosis of
     endotoxemia-related conditions in horses
IN   Brandon, Richard Bruce; Thomas, Mervyn Rees
PA   Athlomics Pty. Ltd., Australia
```

SO PCT Int. Appl., 602pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2007006091	A1	20070118	WO 2006-AU970	20060707

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRAI US 2005-696776P P 20050707
RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
TI Design of bifunctional siRNAs: Combining immunostimulation and gene-silencing in one single siRNA molecule
AB Active suppression of T lymphocyte activation can limit the efficacy of immune surveillance and immunotherapy. Here the authors have explored the possibility of designing bifunctional small interfering RNAs (siRNAs) capable of inducing innate immunity through Toll-like receptors and simultaneously inhibiting the expression of immunosuppressive factors. Using interleukin (IL) 10 as a model, the authors found that liposomal delivery of IL10 siRNAs could efficiently activate the expression of cytokines (e.g. TNF-α, IL6, and IL12) and interferons (e.g. IFN-α) in peripheral blood mononuclear cells (PBMCs) and immature monocyte-derived dendritic cells (iMoDCs). Moreover, the designed siRNAs inhibited IL10 gene expression. Transfection of iMoDCs with either chemical or in vitro transcribed IL10 siRNAs induced their differentiation into mature MoDCs (mMoDCs) characterized by the expression of costimulatory mols. CD80/CD86 and the chemokine receptor CCR7. Lipid delivery of either chemical synthesized or T7-transcribed immunostimulatory siRNAs induced cytokine production However, in contrast to chemical synthesized siRNAs, electroporation of in vitro transcribed siRNAs also induced cytokine production in iMoDCs. Interestingly, IL10 siRNA-transfected iMoDCs were capable of enhancing the response of allogeneic T cells, providing support for the rational design of bifunctional siRNAs as immune modulating therapy.
AN 2006:1331123 CAPLUS <<LOGINID::20070309>>
TI Design of bifunctional siRNAs: Combining immunostimulation and gene-silencing in one single siRNA molecule
AU Furset, Gro; Sioud, Mouldy
CS Department of Immunology, Molecular Medicine Group, Norwegian Radium Hospital, University of Oslo, Oslo, N-0310, Norway
SO Biochemical and Biophysical Research Communications (2007), 352(3), 642-649
CODEN: BBRCA9; ISSN: 0006-291X
PB Elsevier
DT Journal
LA English
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
TI MyD88-dependent and -independent signaling by IL-1 in neurons probed by bifunctional Toll/IL-1 receptor domain/BB-loop mimetics
AB Interleukin (IL)-1β is a pluripotent proinflammatory cytokine that signals through the type-I IL-1 receptor (IL-1RI), a member of the Toll-like receptor family. In hypothalamic neurons, binding of IL-1β to IL-1RI mediates transcription-dependent changes that depend on the recruitment of the cytosolic adaptor protein myeloid differentiation primary-response protein 88 (MyD88) to the IL-1RI/IL-1 receptor accessory protein (IL-1RAcP) complex through homomeric Toll/IL-1 receptor (TIR)-TIR interactions. Through design and synthesis of bifunctional TIR mimetics that disrupt the interaction of MyD88 with the IL-1RI/IL-1RAcP complex, the authors analyzed the involvement of MyD88 in the signaling of IL-1β in anterior hypothalamic neurons. The authors show here that IL-1β-mediated activation of the protein tyrosine kinase Src depended on a MyD88 interaction with the IL-1RI/IL-1RAcP complex. The activation of the protein kinase Akt/PKB depended on the recruitment of the p85 subunit of PI3K to IL-1RI and independent of MyD88 association with the IL-1RI/IL-1RAcP complex. These bifunctional TIR-TIR mimetics represent a class of low-mol.-weight compds. with both an antiinflammatory and neuroprotective potential. These compds. have the potential to inhibit the MyD88-dependent proinflammatory actions of IL-1β, while permitting the potential neuronal survival supporting actions mediated by the MyD88-independent activation of the protein kinase Akt.
AN 2006:459889 CAPLUS <<LOGINID::20070309>>
DN 145:6252
TI MyD88-dependent and -independent signaling by IL-1 in neurons probed by bifunctional Toll/IL-1 receptor domain/BB-loop mimetics
AU Davis, Christopher N.; Mann, Enrique; Behrens, M. Margarita; Gaidarova, Svetlana; Rebek, Mitra; Rebek, Julius, Jr.; Bartfai, Tamas
CS The Harold L. Dorris Neurological Institute and Department of Molecular and Integrative Neurosciences, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Proceedings of the National Academy of Sciences of the United States of America (2006), 103(8), 2953-2958
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
OS CASREACT 145:6252
RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
TI Gene expression profiles in the diagnosis and treatment of Alzheimer's disease
AB Genes showing altered patterns of expression in the brain that are associated with the neurol. changes found in Alzheimer's disease and that can be used in the early diagnosis of the disease, including the incipient form of the disease, are identified. The methods and kits of the invention utilize a set of genes and their encoded proteins that are shown to be correlated with incipient Alzheimer's disease.
AN 2005:902703 CAPLUS <<LOGINID::20070309>>
DN 143:272498
TI Gene expression profiles in the diagnosis and treatment of Alzheimer's disease
IN Landfield, Philip W.; Porter, Nada M.; Chen, Kuey Chu; Geddes, James; Blalock, Eric
PA University of Kentucky Research Foundation, USA
SO PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DT Patent
LA English

```
FAN.CNT 1
     PATENT NO.            KIND   DATE        APPLICATION NO.          DATE
     ---------------       ----   --------    --------------------     --------
PI   WO 2005076939          A2    20050825    WO 2005-US3668           20050209
     WO 2005076939          A3    20060706
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SM
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
PRAI US 2004-542281P        P     20040209


=> d his

     (FILE 'HOME' ENTERED AT 09:24:45 ON 09 MAR 2007)

     FILE 'REGISTRY' ENTERED AT 09:25:17 ON 09 MAR 2007
                EXP ISS-ODN/CN
L1            1 S IMIQUIMOD/CN
L2            1 S RESIQUIMOD/CN
L3            1 S MIZORIBINE/CN

     FILE 'CAPLUS' ENTERED AT 09:26:14 ON 09 MAR 2007
L4          223 S L3/THU
L5           17 S L4 AND CANCER
L6            5 S L5 NOT PY>2004
L7           16 S L2/THU AND CANCER
L8            0 S L7 NOT PY>2004
L9           25 S L2/THU AND INTERFERON
L10          17 S L9 NOT PY>2004
L11          66 S L1/THU AND INTERFERON
L12          34 S L11 NOT PY>2003
L13           3 S L12 AND CANCER

     INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
     AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
     CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
     DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 09:29:54 ON 09 MAR 2007
               SEA OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON
              ---------
              1   FILE BIOSIS
              2   FILE BIOTECHABS
              2   FILE BIOTECHDS
              2   FILE DDFU
              2   FILE DGENE
              2   FILE DRUGU
              1   FILE EMBASE
              1   FILE IFIPAT
              6   FILE MEDLINE
              1   FILE SCISEARCH
              1   FILE TOXCENTER
             37   FILE USPATFULL
              5   FILE USPAT2
              3   FILE WPIDS
              3   FILE WPINDEX
L14             QUE OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON
              ---------
```

```
     FILE 'MEDLINE' ENTERED AT 09:31:25 ON 09 MAR 2007
L15             6 S OLIGONUCLEOTIDE AND (ISS-ODN) AND INTERFERON
L16             0 S L15 AND IMIQUIMOD
L17             0 S IMIQUIMOD AND (ISS-ODN)
L18             0 S RESIQUIMOD AND (ISS-ODN)
L19             0 S BIFUNCTIONAL AND (ISS-ODN)

     FILE 'CAPLUS' ENTERED AT 09:33:06 ON 09 MAR 2007
L20             0 S BIFUNCTIONAL AND (ISS-ODN)
L21             4 S BIFUNCTIONAL AND (TOLL-LIKE)

=> log hold
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    25.68     127.33

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -3.12     -14.04

 SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 09:34:17 ON 09 MAR 2007

Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:SSPTAEXO1623

PASSWORD:
 * * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'CAPLUS' AT 10:37:47 ON 09 MAR 2007
FILE 'CAPLUS' ENTERED AT 10:37:47 ON 09 MAR 2007
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)s

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    25.68     127.33

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -3.12     -14.04

=> s (interferon(w)(alpha or beta))
         75697 INTERFERON
       1671236 ALPHA
       1439661 BETA
L22      13469 (INTERFERON(W)(ALPHA OR BETA))

=> s l22 and cancer
        308330 CANCER
L23       1140 L22 AND CANCER

=> s l32 not py>2002
L32 NOT FOUND
The L-number entered could not be found.  To see the definition
of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s l22 not py>2002
       4999482 PY>2002
```

```
L24       9220 L22 NOT PY>2002

=> s l23 not py>2002
      4999482 PY>2002
L25        711 L23 NOT PY>2002

=> s l25 and exogenous
         94609 EXOGENOUS
L26         11 L25 AND EXOGENOUS

=> d l26 1-11 ti

L26  ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Effect of transfection with human interferon-β
     gene entrapped in cationic multilamellar liposomes in combination with
     5-fluorouracil on the growth of human esophageal cancer cells in
     vitro

L26  ANSWER 2 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Eradication of intraperitoneal and distant tumor by adenovirus-mediated
     interferon-β  gene therapy is attributable to
     induction of systemic immunity

L26  ANSWER 3 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Anticancer drug-induced kidney disorders: Incidence, prevention and
     management

L26  ANSWER 4 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Increasing efficiency of transduction by inhibition of β-interferon
     action and inhibition of neovascularization of tumors with angiostatin
     expression vectors

L26  ANSWER 5 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Endocrine-mediated mechanisms of fatigue during treatment with
     interferon-α

L26  ANSWER 6 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Sensitization of renal carcinoma to radiation using alpha interferon
     (IFNA) gene transfection

L26  ANSWER 7 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Cytokine-induced autoimmune disorders

L26  ANSWER 8 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Modulation of the immunostimulating effect of autologous tumor vaccine by
     anti-TGF-β antibody and  interferon-α  on
     murine MBT-2 bladder cancer

L26  ANSWER 9 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Neuroimmunotherapy of human neoplasms with melatonin and antitumor
     cytokines

L26  ANSWER 10 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   In vitro modulation of the invasive and metastatic potentials of human
     renal cell carcinoma by interleukin-2 and/or interferon-
     alpha gene transfer

L26  ANSWER 11 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Tumor-specific lysis of human renal cell carcinomas by tumor-infiltrating
     lymphocytes: modulation of recognition through retroviral transduction of
     tumor cells with interleukin 2 complementary DNA and exogenous
     α interferon treatment
```

=> d l26 4 5 6 8 9 11 ti abs bib

L26 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
TI Increasing efficiency of transduction by inhibition of β-interferon action and inhibition of neovascularization of tumors with angiostatin expression vectors
AB A method of increasing the effectiveness of virus-mediated gene therapy by inhibiting β-interferon function is described. The method is specifically intended for use with adenovirus-based vectors. Inhibitors include antibodies to interferon β or antisense DNA or ribozymes inhibiting gene expression. The method can be used to improve effectiveness of gene therapy of genetic diseases and of cancers. Methods for the treatment of neovascularization-related diseases, for examples, cancer, by the production in vivo of angiostatin, which inhibits the formation of new blood vessels are also described. In particular embodiments, this is accomplished by transduction of macrophages ex vivo with a GM-CSF gene, thereby inducing the secretion of macrophage metalloelastase, which converts plasminogen to angiostatin. The transduced macrophages, when administered, naturally home to tumor sites to effectively localize the therapeutic effect. Expts. in which macrophages were transformed with reporter gene expression constructs demonstrated that neutralization of interferon β in the medium with monoclonal antibodies increased the level of expression of the reporter. Addition of exogenous β-interferon decreased levels of expression.
AN 1998:352956 CAPLUS <<LOGINID::20070309>>
DN 129:24138
TI Increasing efficiency of transduction by inhibition of β-interferon action and inhibition of neovascularization of tumors with angiostatin expression vectors
IN Fidler, Isaiah J.; Dong, Zhongyun; Kumar, Rakesh
PA Board of Regents, the University of Texas System, USA
SO PCT Int. Appl., 182 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9822605	A1	19980528	WO 1997-US21475	19971119
	W: CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2275438	A1	19980528	CA 1997-2275438	19971119
	EP 963440	A1	19991215	EP 1997-950669	19971119
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001505205	T	20010417	JP 1998-523953	19971119
PRAI	US 1996-31330P	P	19961120		
	WO 1997-US21475	W	19971119		

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
TI Endocrine-mediated mechanisms of fatigue during treatment with interferon-α
AB A review with 95 refs. Fatigue occurs in more than 70% of patients treated with interferon-α (IFN-α) and is the most problematic toxicity associated with IFN-based immunotherapy. Abundant evidence suggests that immune-mediated endocrine disease occurs during IFN-α therapy, which may contribute to the etiol. of fatigue. Autoimmune thyroid disease is a well-recognized consequence of IFN-α therapy and may be mediated by the induction of IFN-γ production by lymphocytes. Administration of exogenous IFN-γ has been associated with upregulation of class II major histocompatibility antigens in

the thyroid and the development of thyroiditis. Interferon-. alpha. also stimulates the production of interleukin-6; both interleukin-6 and IFN-γ have specific effects on thyrocyte function. There also is evidence suggesting that IFN-α initiates a cytokine cascade that effects the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes, thus affecting regulation of glucocorticoid and sex steroid hormone secretion, but the clin. significance of these observations has not been established. Although endocrine disease will not explain the occurrence of fatigue symptoms in all patients, there is clear evidence that hormonal deficiency syndromes occur in a relatively large portion of patients receiving systemic IFN-α therapy. Most importantly, the possibility of hypothyroidism must be considered; however, diagnosis of hypothyroidism in cancer patients is complicated by the occurrence of the "sick euthyroid syndrome.". Clin. recommendations for assessment and treatment of IFN-α-induced fatigue are offered. Most importantly, measurements of TSH and antithyroid autoantibodies should be used to evaluate thyroid status. Acknowledging the limitations of current clin. data, adrenal- and gonadal-axis dys-function also must be considered in patients with IFN-α-induced fatigue.

AN 1998:146116 CAPLUS <<LOGINID::20070309>>
DN 128:242673
TI Endocrine-mediated mechanisms of fatigue during treatment with interferon-α
AU Jones, T. Hugh; Wadler, Scott; Hupart, Kenneth H.
CS Departments of Medicine and Pharmacology, Royal Hallamshire Hospital and University of Sheffield, Sheffield, UK
SO Seminars in Oncology (1998), 25(1, Suppl. 1), 54-63
CODEN: SOLGAV; ISSN: 0093-7754
PB W. B. Saunders Co.
DT Journal; General Review
LA English
RE.CNT 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
TI Sensitization of renal carcinoma to radiation using alpha interferon (IFNA) gene transfection
AB The rationale for this study was that local delivery of interferon -alpha (IFN-α) by gene transfection may be of value during radiotherapy. To investigate the feasibility of this approach, cells of the human renal carcinoma cell line R11 were transfected with the IFNA gene and evaluated for radiation responses in vitro by clonogenic assays. R11 cells expressing IFN-α after gene transfection were more sensitive to radiation than R11 control cells (SF2 = 0.33 and 0.51, resp.). In addition to increasing radiosensitivity, IFNA gene transfection slowed cellular growth and reduced the plating efficiency in clonogenic assays. The addition of exogenous rhIFN-α to cells at different times relative to irradiation showed that its presence during the postirradn. period was critical for radiosensitization, but repair of sublethal damage did not seem to be affected. No apoptosis of R11 cells was found 1-5 days after exposure to 2-25 Gy with or without IFN-α. Extensive formation of multinuclear giant cells was present beginning 2 days after irradiation; however, IFN-α did not cause any major alterations in the yield of radiation-induced giant cells. These studies suggest that gene transfection might be an effective means of delivering IFN-α for clin. use in radiotherapy of cancer.
AN 1997:708948 CAPLUS <<LOGINID::20070309>>
DN 128:31917
TI Sensitization of renal carcinoma to radiation using alpha interferon (IFNA) gene transfection
AU Gyljuasen, Randi G.; Belldegrun, Arie; Tso, Cho-Lea; Withers, H. Rodney; McBride, William H.
CS Dep. Radiation Oncol., Univ. California, Los Angeles, CA, 90095, USA

SO Radiation Research (1997), 148(5), 443-448
CODEN: RAREAE; ISSN: 0033-7587
PB Radiation Research Society
DT Journal
LA English
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
TI Modulation of the immunostimulating effect of autologous tumor vaccine by anti-TGF-β antibody and interferon-α on murine MBT-2 bladder cancer
AB Our aims were to: a) elucidate whether MBT-2 cells, lethally irradiated or nonirradiated, express TGF-β1 mRNA and secrete TGF-β1 protein, and b) to investigate whether the adverse effects from IRMBT-2-secreting TGF-β1 in the tumor vaccine can be abrogated by exogenous addition of monoclonal anti-TGF-β1 antibody and/or IFN-α. Using the Northern hybridization anal. and the two-antibody sandwich ELISA, we demonstrate that both irradiated IRMBT-2 and nonirradiated MBT-2 cells secrete TGF-β1. The effect of anti-TGF-β and/or IFN-α were studied by an in vitro splenocyte proliferation assay and in vivo tumor rechallenge study on day 17-TBM. Both IRMBT-2 and splenocytes from day 17-TBM secrete TGF-β1 which can express suppression of the proliferation of the splenocytes from day 17-TBM. This suppression can be partially reversed by the simultaneous addition of both anti-TGF-β and IFN-α, either alone being insufficient. The result of the in vivo tumor rechallenge study on day 17-TBM reveals that a lower tumor outgrowth incidence can be obtained in groups of mice treated with postoperative vaccination with anti-TGF-β modified tumor vaccine with or without an addnl. administration of IFN-α. Apart from TGF-β, MBT-2 cells, both irradiated and nonirradiated, may also secrete other suppressive factors that adversely downregulate the immune response of TBM which can not then be adequately reversed by IFN-α.
AN 1997:307397 CAPLUS <<LOGINID::20070309>>
DN 126:342432
TI Modulation of the immunostimulating effect of autologous tumor vaccine by anti-TGF-β antibody and interferon-α on murine MBT-2 bladder cancer
AU Tzai, Tzong-Shin; Shiau, Ai-Li; Lin, Chein-Sheng; Wu, Chao-Liang; Shinn-Nan Lin, Johnny
CS Department of Urology, Medical College, National Cheng Kung University, Tainan, Taiwan
SO Anticancer Research (1997), 17(2A), 1073-1078
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
TI Neuroimmunotherapy of human neoplasms with melatonin and antitumor cytokines
AB The biol. and antitumor activities of cytokines have appeared to be modulated by the psycho neuroendocrine system, mainly by the pineal hormone melatonin (MLT) and opioid peptides. In particular, MLT has been seen to amplify IL-2 anticancer action and to reduce its toxicity. The rationale of MLT use in association with IL-2 cancer immunotherapy may be summarized, as follows: (1) amplification of IL-2 biol. activity by enhancing TH2 lymphocyte response and by antagonizing macrophage-mediated suppressive events; (2) inhibition of production of tumor growth factors, which stimulate cancer cell proliferation by counteracting lymphocyte-mediated tumor cell destruction; (3) maintenance of a circadian rhythm of MLT, which is often altered in human neoplasms and influenced by

cytokine exogenous injection. The neuro immunotherapy with s.c. low-dose IL-2 (3 million IU/day) and pharmacol. doses of MLT (40 mg/day orally) in the evening has appeared to be effective in tumor histotypes resistant either to IL-2 alone, or to chemotherapy. At present, 230 patients with advanced solid tumors and life expectancy less than 6 mo have been treated. Objective tumor regressions were in 44 patients (18%), mainly in patients with lung cancer, hepatocarcinoma, cancer of pancreas, gastric cancer, colon cancer . A survival longer than 1 yr was achieved in 95/230 (41%) patients. Toxicity was low in all patients, who were treated as home therapy. Moreover, preliminary data suggest that MLT synergizes also with TNF and interferon alpha, by reducing their toxicity.

AN 1997:36277 CAPLUS <<LOGINID::20070309>>
DN 126:58707
TI Neuroimmunotherapy of human neoplasms with melatonin and antitumor cytokines
AU Lissoni, P.
CS Division of Radiation Oncology, San Gerardo Hospital, Milan, Italy
SO International Journal of Thymology (1996), 4(Suppl. 1), 84-87
CODEN: IJTYEI; ISSN: 0943-1675
PB Thymus Medizinischer Fachbuchverlag
DT Journal
LA English

L26 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
TI Tumor-specific lysis of human renal cell carcinomas by tumor-infiltrating lymphocytes: modulation of recognition through retroviral transduction of tumor cells with interleukin 2 complementary DNA and exogenous α interferon treatment
AB Two cytotoxic effector cell populations were isolated from a patient with renal cell carcinoma. The tumor-infiltrating lymphocytes comprised a population of highly specific, major histocompatibility complex-restricted, cytotoxic T lymphocytes (CTL). An autologous non-major histocompatibility complex-restricted lymphokine-activated killer (LAK) cell population was generated by culturing the peripheral blood lymphocytes with high doses of recombinant interleukin 2 (rIL-2). The capacity of these two effector cell types to lyse cytokine-modulated autologous tumor cells was compared in vitro. A complementary DNA for rIL-2 was introduced into the tumor cells by retroviral transduction, and tumor cells secreting low doses of rIL-2 were isolated. The CTL recognition of these tumor cells was enhanced, compared to unmodified tumor cells, whereas LAK cell recognition was unchanged or slightly reduced. Pretreatment of tumor cells with exogenous α interferon led to an up-regulation of some major histocompatibility complex class I mols. and to slightly better recognition by the CTL; little effect on LAK cell recognition was observed CTL were 50-150 fold more effective than LAK cells in lysing autologous tumor cell lines or clones modulated with both rIL-2 and α interferon. The assessment of a patient's cytotoxic immune capacity directed against genetically modified autologous tumor cells in vitro provides important insight for cytokine-mediated gene therapy of cancer.
AN 1993:624146 CAPLUS <<LOGINID::20070309>>
DN 119:224146
TI Tumor-specific lysis of human renal cell carcinomas by tumor-infiltrating lymphocytes: modulation of recognition through retroviral transduction of tumor cells with interleukin 2 complementary DNA and exogenous α interferon treatment
AU Schendel, Dolores J.; Gansbacher, Bernd
CS Inst. Immunol., Ludwig-Maximilians-Univ., Munich, 8000/2, Germany
SO Cancer Research (1993), 53(17), 4020-5
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English

```
=> s (interferon(1a)(alpha or beta))
         75697 INTERFERON
       1671236 ALPHA
       1439661 BETA
L27      20039 (INTERFERON(1A)(ALPHA OR BETA))

=> s l27 and cancer
        308330 CANCER
L28       1490 L27 AND CANCER

=> s l28 not py>2002
       4999482 PY>2002
L29        949 L28 NOT PY>2002

=> s l29 and exogenous
         94609 EXOGENOUS
L30         14 L29 AND EXOGENOUS

=> s l30 not L26
L31          3 L30 NOT L26

=> d l31 1-3 ti

L31  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Towards defining roles and relationships for tenascin-C and TGFβ-1 in
     the normal and neoplastic urinary bladder

L31  ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Interferon-γ reduces tumor-induced Ia- macrophage-mediated
     suppression: role of prostaglandin E2, Ia, and tumor necrosis
     factor-α

L31  ANSWER 3 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Constitutive production of interleukin 6 by ovarian cancer cell
     lines and by primary ovarian tumor cultures


=> d l31 ti abs bib

L31  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Towards defining roles and relationships for tenascin-C and TGFβ-1 in
     the normal and neoplastic urinary bladder
AB   Tenascin-C (TN-C) is an extracellular matrix glycoprotein expressed along
     epithelial/stromal boundaries during tissue remodeling events, such as
     those that occur during morphogenesis, wound healing, and tumor invasion.
     Using clin. specimens and a range of in vitro models that simulate
     homeostasis, wound healing, and malignant progression, this study sought
     to establish the patterns of TN-C expression in normal and neoplastic
     bladder and to determine the role of exogenous transforming growth
     factor β-1 (TGFβ-1), interleukin-4 (IL-4), basic fibroblast
     growth factor (bFGF), tumor necrosis factor alpha (TNFα ),
     and interferon gamma (IFNγ) in the induction of TN-C
     expression by bladder uro-epithelial cells.  The findings indicate that
     normal urothelial cells may express TN-C, with both TGFβ-1 and IL-4
     able to induce expression.  TN-C was not expressed in neoplastic
     urothelium, although both TN-C and TGFβ-1 may be involved in tissue
     remodeling during papillary tumor formation and invasion.  Furthermore,
     the urothelium of high-grade papillary tumors and carcinoma in situ
     specimens exhibited little TGFβ-1 immunoreactivity, compared with the
     urothelium of low-grade tumors and normal specimens, suggesting an association
     between TGFβ-1 expression and urothelial differentiation.  A tumor
     invasion model, in which established bladder cancer cell lines
     were seeded onto a normal bladder stroma, corroborated the evidence from
```

the clin. specimens and demonstrated that TN-C was strongly expressed around foci of stromal invasion. Thus, TN-C immunoreactivity may provide an addnl. tool in the assessment of early stromal invasion in bladder cancer.

AN 2002:892826 CAPLUS <<LOGINID::20070309>>
DN 138:185087
TI Towards defining roles and relationships for tenascin-C and TGFβ-1 in the normal and neoplastic urinary bladder
AU Booth, Catherine; Harnden, Patricia; Selby, Peter J.; Southgate, Jennifer
CS Jack Birch Unit of Molecular Carcinogenesis, Department of Biology, University of York, York, YO10 5YW, UK
SO Journal of Pathology (2002), 198(3), 359-368
CODEN: JPTLAS; ISSN: 0022-3417
PB John Wiley & Sons Ltd.
DT Journal
LA English
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/824833

Europäisches Patentamt
European Patent Office
Office européen des brevets

Description of DE19811313	Print	Copy	Contact Us	Close

Result Page

p1 3-6

The invention concerns a procedure for the determination of the enzymatic activity of Inosin-5' mono phosphate dehydrogenase (IMPDH) in the blood of patients as well as the use of this procedure for the therapeutic monitoring as well as for the monitoring of the immunsuppressiven status of patients, who were treated with IMPDH inhibitors. In addition the subject of the invention is a test kit for the execution of the procedure according to invention.

The enzyme Inosin 5 ' - mono phosphate dehydrogenase (IMPDH: NAD Oxidoreductase, E.C. 1.2.1.14) is the key enzyme of the biosynthesis way of guanine Nucleotiden. In a NAD dependent reaction one oxidizes to Inosin 5 ' - mono phosphate (IMP) by IMPDH to Xanthosin 5 ' - mono phosphate (XMP). Proliferating cells need high quantities of Guanosin triphosphate (GTP), so that the IMPDH catalyzed reaction becomes the speed-determining step during the supply from GTP. The biosynthesis of guanine Nucleotiden becomes schematic in Fig. 1 represented

In human fabrics two forms of IMPDH are distinguishable. Structure and catalytic characteristics of both forms, when type designates I and type II, are well characterized. Northern Blot analyses from mRNA, isolated from different fabric, resulted in that both ISO forms are exprimiert (Senda M, Natsumeda, Y.: Tissue differential Expression OF Two Distinct of gene for human IMP Dehydrogenase (E.D.1.1.1.205), Sciences 54, No. would run. 24, 1917-1926 (1994)). Findings however, according to which in proliferating cells quantitatively type II-IMPDH outweighs, in resting cells against it type I, led to the classification into the ?konstitutive type I-IMPDH? and the ?inducable type II-IMPDH? (Nagai, M., Natsumeda, Y., Weber, G.: Proliferation linked regularization OF type II IMP Dehydrogenase of genes in human normally Lymphocytes and HL-60 Leukemic Cells, CAN cerium Research 52, 258-261 (1992)).

In tumor cells and proliferating Lymphozyten substantially increased enzyme activities could be measured (Konno Y, Natsumeda Y, Nagai M, Yamaji Y, Ohno S, Suzuki K, Weger G: Expression OF human IMP Dehydrogenase of type I and II in Escherichia coli and distribution in human normally Lymphocytes and Leukemic Cell LINEs, The journal OF Biological Chemistry 266, No. 1, 506-509 (1991); Collart FR, Huberman E: Expression OF IMP Dehydrogenase in Differentiating HL-60 Cells, Blood 75, No. 3, 570-576 (1990); Collart FR, Chupp CB, Mirkin BL, Huberman E: Increased Inosine-5' of phosphates Dehydrogenase of genes Expression in solvently tumor tissue and tumor Cell LINEs, CAN cerium Research 52, 5826-5828 (1992); Kiguchi K, Collart FR, Henning Chubb C, Huberman E: Induction OF Cell deviation in Melanoma Cells by Inibitors OF IMP Dehydrogenase: Old person-talk Patterns OF IMP Dehydrogenase Expression and Acitvity, Cell Growth & deviation 1, 259-270 (1990); Stadler PB, Pennacchi J, Sherley JL: Inosine-5' of mono phosphates Dehydrogenase Activity is Maintained in Immortalized Murine Cells Growth Arrested by serum Deprivation, Advan of enzymes Regul 34, 91-106 (1994); Huberman E, Glesne D, Collart F: Regularization and Role OF Inosine-5' of mono phosphates Dehydrogenase in Cell Replication, Malignant transformation and deviation, Advances in experimental Medicine and Biology 370, 741-746 (1995)). Therefore the medicine-material-obtained inhibition of the IMPDH is a possible starting point (?target?) to the therapy of cancer illnesses and in particular to the Immunsuppression after Organtransplantation.

3.-4

The concept of the Immunsuppression by IMPDH inhibition bases on the fact that with inhibition of the IMPDH aimed the pro running ration for the immune answer of the responsible persons t and B-Lymphozyten can be restrained, since both cell types cannot activate ?Salvage pathway? to the Nucleotidsynthese, while other cells can fill up the GTP pool by the alternative supplying way (Ransom, JT: Mechanism OF Action OF Mycophenolate Mofetil, Therapeutic Drug monitoring 17, No. 6, 681-684 (1995)).

With Bredinin TM (active substance: Mizoribine) and CellCept TM (active substance: Mycophenolat mofetil) were developed two IMPDH inhibitors clinically and are successfully used today to the immunsupressiven therapy, whereby Bredinin is certified TM so far only in Japan. A further active substance, VX-497 (press release of the companies Vertex, Cambridge, mA, 2. December 1996), which is to cause substantially fewer side effects compared with the IMPDH inhibitors used so far, should be also for the treatment of chronic autoimmune illnesses, like asthma, Psoriasis, rheumatoide Arthritis and systemic Lupus erythematodes, suitable.

Unfavorable way is based the dosage of these immunsuppressiven medicines alone on experiences of clinical examinations and on their pharmakokinetischen characteristics. Individual dose adjustments are not at present possible, since after today's level of knowledge the quantitative determination of the active substance in blood does not permit a statement about the immunsuppressiven status. Therefore the determination of the IMPDH activity was discussed as pharmacodynamic parameters as possible alternative to the optimization of the therapy with IMPDH inhibitors in several publications (Langman LJ, put-corrode DF, Yatscoff RW: Pharmacodynamic Assessment OF Mycophenolic Acid Induced Immunosuppression by Measuring IMP Dehydrogenase Activity, Clin Chem 41, No. 2, 295-299 (1995); Langman LJ, Shapiro AJ, Lakey blank, put-corrode DF, Kneteman Nm, Yatscoff RW: Pharmacodynamic assessment OF mycophenolic acid induced immunosuppression by measurement OF IMP dehydrogenase in A canine model, Transplantation 61, 87-92 (1996); Langman LJ, put-corrode DF, Halloran PF, Yatscoff RW: Pharmacodynamic Assessment OF Mycophenolic Acid Induced Immunosuppression in Renal Transplant Recipients, Transplantation 62, 666-672 (1996); Langman LJ, Nakakura H, Thliveris, put-corrode DF, Yatscoff RW: Pharmacodynamic monitoring OF Mycophenolic Acid in Rabbit

Heterotopic Heart Transplant Model, Therapeutic Drug monitoring 19, 146-152 (1997)).

In the past different methods were published for the measurement of the IMPDH Enzymaktivität. These are arranged in table 1.

Table 1

Published procedure for the determination of the IMPDH activity
EMI4.1

The methods [1] - [6] are more near described in the following literature places:
Method [1]: Hager PW, Collart FR, Huberman E, Mitchell B: Recombinant human Inosine of mono phosphates Dehydrogenase type I and type II of protein, Biochemical Pharmacology 49, No. 9, 1323-1329 (1995);
Method [2]: Ikegami T, Natsumeda Y, Welor G: Direct assay method for inosine 5 ' - mono phosphates dehydrogenase activity, Anal Biochem 150, 155-166 (1985);
Method [3]: Proftitt blank, Pathak VK, Villacorte DG, Presant APPROX.: Sensitive radiochemical assay for inosine 5 ' - mono phosphates dehydrogenase and determination OF activity into murine tumor tissue extracts, CAN cerium Res 43, 1620-1623 (1983);
Method [4]: Langman LJ, put-corrode DF, Yatscoff RW: Pharmacodynamic Assessment OF Mycophenolic Acid Induced Immunosuppression by Measuring IMP Dehydrogenase Activity, Clin Chem 41, No. 2, 295-299 (1995);
Method [5]: Balzarini JB, de Clercq E: Assay method for monitoring the inhibitory effects on of antimetabolites on the activity OF inosine dehydrogenase in intact human CEM of lymphocytes, Biochemistry 287, 785-790 (1992);
Method [6]: Montero C, Duley, fair bank LD, McBride MT, Micheli V, Cant AJ, Morgan G: Demonstration OF induction OF erythrocyte inosine mono phosphates dehydrogenase activity in Ribavirin treated patients using A high performance liquid chromatography linked method., Clin Chem Acta 238, 169-178 (1995).

The procedure of Balzarini and de Clercq (method [5]), who on the use of [<3> H] - marked Hypoxanthin or [<3> H] - to marked Inosin is based and due to the diaphragm freedom of movement of Hypoxanthin (HX) and Inosin (Ino) with intact cells is accomplished, of the working group of Yatscoff one developed further [method [4]) and presented as possibility for the pharmacodynamic monitoring. The authors accomplished the investigations however in cell parliamentary groups won from full blood and reported that the activity determined in this Kompartiment represents also the activity existing in Lymphozyten. From own investigations Anmelderin comes out however that this statement applies to full blood of healthy test subjects and can thus also to the described animal experiments, within whose frameworks an IMPDH inhibitor was uniquely given apply. With transplant ion patients however, to who an IMPDH inhibitor is daily given, this findings could not be confirmed by the test results of the Anmelderin surprisingly.

A further disadvantage is to be seen in the fact that Hypoxanthin (HX) is also substrate of the ubiquitously occurring Xanthin Oxidase (XO). During the XO-obtained oxidation from HX to Xanthin and to urine acid from the substrate [2,8< 3> H2] - HX is likewise continued to set free <>3 H. If this reaction to larger extent should run off, measured tritium represents not only the IMPDH, but also the XO-activity.

The method [4] is not therefore suitable for the IMPDH determination of activity in transplant ion patients treated with IMPDH inhibitors. A cause for this is the fact that the IMPDH activity is very small in Erythrocyten of healthy persons, rises under therapy with IMPDH inhibitors however on a multiple of the base value and completely overlays the activity existing in Lymphocyten. In addition require the methods [4] and [5] the employment of tritiierter connections, which is health precarious and in addition requires complex safety precautions. Same applies to the use of the expensive carbon isotope <14> C in accordance with the procedures after the methods [2] and [3]. The method [1] requires the complex cleaning of the IMPDH and the method [6] measures only the IMPDH activity in Erythrozyten. The methods [4] and [5] in addition possess the conceptional disadvantage that due to the used substrates (Hypoxanthin and Inosin) those are included the actual IMPDH catalyzed reaction upstream enzymatic conversions in the test. Disturbances of these upstream enzymatic conversions save the potential danger of a misinterpretation of the determined results of measurement.

Therefore the task is appropriate for the invention to reason to make a procedure available for the determination of the activity of the enzyme IMPDH which avoids the disadvantages of the state of the art described above.

The available task surprisingly solved by supply of a procedure for the determination of the enzymatic activity of IMPDH in the blood of a mammal, insbe< DP N=7> separate humans, which is characterized by the fact that one accomplishes mononuclear cells with a Lysat containing of a cell parliamentary group from the blood of the mammal a IMPDH catalyzed enzymatic reaction in a radioactivity-free reaction beginning and from the quantity of a non-radioactive reaction product the IMPDH activity developing formed per time unit thereby in the blood of the mammal determined.

The used reaction beginning covers thereby at least a non-radioactive substrate for IMPDH and if necessary at least a non-radioactive Cosubstrat for IMPDH.

Particularly prefers assigned substrate is Inosin-5' mono phosphate (IMP), which is converted from IMPDH into presence of the Cosubstrats Nikotinamidadenindinukleotid (NAD) under education from NADH into Xanthosin-5' mono phosphate (XMP). From the quantity of formed XMP (i.e. Product) and/or. NADH (i.e. Coprodukt) can be reckoned back afterwards on the IMPDH activity in the examined blood test. The exact evaluation is described later by indication in detail by calculation formulas. The available invention is not limited however to the use of IMP as substrate. The use of non-radioactive IMP analogues, D is just as conceivable. h. of connections, which are converted likewise by IMPDH.

In accordance with a particularly preferred execution form of the invention become the Lysat as non-radioactive substrate IMP and as non-radioactive Cosubstrat NAD in suitable concentrations, like z. B. within the range of 0,1 to 10 mm, added. A preferential NAD and/or. IMP concentration is appropriate for z. B. with approximately 0.25 mm. The selected substrate and/or. Cosubstratkonzentration should be so selected anyhow that in the respective observation period, like z. B. 5 min to 2 h, the rise of XMP and/or. NADH, in the reaction beginning linear runs.

Preferably one leads the IMPHD catalyzed enzymatic reaction in addition in presence of Allopurinol and/or EDTA accomplishes, in order falsifications of the results of measurement if necessary to prevent (which will later still more

near be described).

The evaluation of the proof procedure takes place preferably via the fact that one the quantity of a non-radioactive product formed with the enzymatic reaction (i.e. Reaction product of the assigned substrate) and/or a not-radioactive Coprodukts (i. e. Reaction product of the assigned Cosubstrats) directly or after their further chemical or enzymatic conversion, preferably quantitatively, determines. A chemical or enzymatic conversion is recommendable whenever thereby a simpler, more troublefree or more sensitive proof procedure for the substance which can be analyzed is made possible.

In accordance with a particularly preferred execution form one preferably determines the formed XMP during the evaluation of the procedure according to invention, according to chemical Deglycosidierung to Xanthin and determination of the Xanthinmenge. Another preferential execution form covers the determination of the formed NADH's.

The quantitative determination of the Analyten examined in each case can take place thereby chromatographisch, photometrically, fluorimetrisch or luminometrisch. The Xanthinbestimmung takes place preferably chromatographisch; the NADH regulation takes place against it preferably photometrically.

The quantity of formed NADH, proportional to the formed XMP quantity, can be determined for example spektrophotometrisch by determination of the extinction with 340 Nm. Further the possibility exists of determining the formed NADH quantity directly by Fluorimetrie. For this purpose one induces with an excitation wavelength of z. B. 340 Nm in the reaction mixture fluorescence and determines with a wavelength of z. B. 460 Nm the emitted light with the help of a Fluorimeters (see. z. B. Gleeson, M. et al., Clinica Chimica Acta, 166 (1987) 163-169). For the increase of the detector response it is conceivable in addition to accomplish a coupled optical test. A suitable test system represents for example a bioluminescence test system, based on the enzymes Flavindehydrogenase and bacterial Luciferase. With this system the resulting NADH Reduktionsäquivalente is transferred with the help of the enzyme Flavindehydrogenase in presence of Flavinmononukleotid (FMN) in FMNH2. Bacterial Luciferase converts FMNH2 in presence of atmospheric oxygen and a langkettigen, aliphatic aldehyde under light emission. The emitted light is provable and the formed NADH proportional with approximately 490 Nm (see. Cross-beams, D. J. and Peck, H. Analytical Biochemistry (1983) Longman Group Ltd. Hrsg, S. 272. FF; How/as country, E. et al., J. Clin. Chem. one. Clin. Biochem. (1985), 23, 99-103).

The NADH education cannot only being accomplished like above described in solution. Rather it is also conceivable, NAD or suitable analogues in actually well-known way to a stationary phase, like z. B. a Teststreifen or a sample tube to immobilize. The IMPDH Nachweisreaktion described above is then accomplished in presence of the immobilized NAD's. For the completion of the test the reaction beginning is separated from the immobilized NADH containing phase and their NADH content becomes in a suitable analyzer, z. B. photometrically, determines.

A further possibility for the determination of the formed NADH's exists NADH Oxidasekatalysierter conversion in its more enzymatically, to NAD under formation of hydrogen peroxide. The formed peroxide quantity is proportional to the formed NADH and can be determined in different way. For example formed hydrogen peroxide can be proven by means of an oxidative clutch reaction, as for example described in the EP-A-0 530,732. In addition, it is conceivable, which formed hydrogen peroxide with a specific hydrogen peroxide electrode to quantify (see. z. B. Tabata, M., et al., Analytica Chimica Acta (1994), 298, 113-119). Another possibility, NADH will quantify from Pandey in Anal. Biochem. (1994), 221, 392-396 described. It is suggested, the NADH education with an electro-chemical, by Tetracyanochinodimethan (TCNQ) obtained, oxidation reaction to couple, whereby TCNQ is embedded in a graphite paste electrode.

For the further improvement of the proof procedures for NADH, described above, the immobilization is individual or all at the respective proof reaction took part enzymes conceivablly. An immobilization does not only possess the advantage that the detector response of the respective reaction is increased. An immobilization increases in addition the life span of the used enzymes and makes their re-use possible. This is from special use for an automation of the proof procedure. Hochsensitive NADH Nachweisverfahren, based on different immobilized enzyme systems for example described of Girotti, S. et al. in journal OF Bioluminescence and Chemiluminescence, (1989) 3, 41-45; Roda, et al., in journal OF Bioluminescence and Chemiluminescence, (1989) 4, 423-435; and Ugarova, et al., Anal. Biochem (1988) 173, 221-227.

An automated evaluation of the IMPDH test according to invention could, without being limited to it, be accomplished for example according to the following pattern:
After stopping the reaction, z. B. by addition of acid, the NADH haltige reaction mixture (sample volume z becomes. B. 5-100 : 1) by means of a Samplers on a before-conditioned stationary phase, like z. B. a micro column, laid on. On the stationary phase, like z. B. Agar eye, Sepharose or glass beads, is (are) () the enzyme (e), necessary for the NADH conversion, like z. B. NADH Oxidase, Flavindehydrogenase, bacterial Luciferase, immobilizes.

If one prefers an electro-chemical NADH proof which is based on peroxide, then one uses immobilized NADH Oxidase as stationary phase. The hydrogen peroxide formed with the passage by the stationary phase arrives into a flow cell equipped with a hydrogen peroxide electrode. The electric current flowing thereby is noted and from this the NADH concentration is determined (see. Tabata, M. et al. A.A.O.). After conclusion of the measurement stationary phase and Messzelle by washing and Äquilibrieren for a new test cycle are prepared. Peroxide could likewise by suggestion of chemistry luminescence, like of DeLuca, M. and McElroy, W. D. in Methods Enzymol (1986), 133, 331-584, to be described, quantified. It would have for example conceivable to replace above peroxide electrode by a Chemiluminezenzreaktor which immobilized peroxidase, like z. B. Merettich peroxidase, contains. The peroxide mixture is shifted before introducing into the reactor with Luminol haltigem buffer. The intensity of the light emitted with expiration of reaction is then photometrically determined.

Suitable devices for an automated photometric NADH analysis which is based on bioluminescence are for example of Roda et al., A.A.O. or Girotti et al., A.A.O. described. Girotti et al., describe in a Luminometer used bioluminescence reactor. This covers as stationary phase a nylon hose with coimmobilisierter bacterial Luciferase and Flavindehydrogenase. The NADH haltige mixture becomes after mixing with the Cofaktoren (FMN), necessary for the proof reaction, and substrates (Decanal) by the bioluminescence reactor led and the intensity of the emitted light determines. In modification of it also a two-stage reaction guidance over two different stationary phases is, like of Roda et al. suggested, applicably. One shifts and leads the NADH haltige mixture first with a FMN haltigen buffer it over a first

stationary phase to which Flavindehydrogenase is immobilized. The FMNH2-haltige Eluat resulting thereby one mixes containing buffers with a bioluminescence substrate and leads this mixture into the bioluminescence reactor, which contains only Luciferase in immobilized form. After completion of the measurement the stationary phases are rinsed and äquilibriert and to be available for a renewed test cycle.

In accordance with a preferential execution form of the invention after stopping the reaction the formed XMP in the sour one is deglycosidiert if necessary and under heat supply to Xanthin and in this way formed Xanthinmenge chromatographisch, in particular by HPLC chromatography is quantitatively seized. The unwanted education catalyzed by Xanthinoxidase is prevented by addition from Allopurinol to the reaction beginning by Xanthin from Hypoxanthin.

In the following sections the production of the blood tests, the necessary sample preparation, which can be examined, becomes which and the evaluation of the proof procedure according to invention describes execution more near:
With the withdrawal of the blood test it should be paid attention to the fact that the withdrawal tube contains a anti-coagulating substance, for example EDTA or a left-Heparin, in order to avoid a coagulating of the blood.

The isolation mononuclear cells of the containing parliamentary group takes place in usual procedures, for example via Zentrifugation and Abdekantieren of the blood plasma from the incoagulable made blood test. By ?mononuclear cells? one understands Lymphozyten and Monozyten according to invention.

In a preferential execution form one isolates the mononuclear cells containing parliamentary group in such a way that not-mononuclear cells are removed and in such a way won sample essentially freely from Erythrozyten, Granulozyten and Thrombozyten, in particular essentially free from Erythrozyten are. Plasma is separated likewise with this procedure variant. Suitable procedures for this are for example Dichtezentrifugation over gradients from Histopaque a TM or Dichtezentrifugation over gradients from Ficoll and Metrizimid (Hypaque) or special method, for example biomagnetic Separation.

An aliquot can be inferred according to invention isolated from the cell parliamentary group if necessary, in order to determine the cell number in usual way, as for example in a Thoma chamber according to trypan blue colouring.

In a particularly preferred execution form of the procedure according to invention the erythrocyte-EN-free mononuclear cell parliamentary group before the execution of the Zelllyse in plasma is resuspendiert, which became to receive from the same mammal (animal or humans), like the mononuclear cells. In particular the Resuspendierung takes place in the plasma projection the same blood test, which contained also the mononuclear cells. This ensures that the according to invention supplies an ex-vivo-activity of the IMPDH to vitro accomplished procedures. This is above all of importance if the sample Donor were treated with an IMPDH inhibitor, which is predominantly present in the blood bound to plasma proteins. This is investigations in particular according to the Anmelderin with Mycophenolat mofetil and/or. its free active substance Mycophenolsäure (MPA) the case. The concentration to free Mycophenolsäure becomes, as in Fig. 2 represented, both of the concentration at albumin (HSA) and of the concentration at Mycophenolsäure Glucuronid (MPAG), which affects main metabolites of MPA. Beyond that it is to be accepted generally that the plasma concentration of the active substance given in each case affects the intrazelluläre IMPDH Inhibitorkonzentration and with it the IMPDH activity significantly, so that also for this reason the Resuspendierung of the cells is of advantage in plasma special.

The determination of the ex-vivo-activity with in above way the manufactured cell Lysat effected prefers in a non-radioactive reaction beginning, how described above. It is however likewise conceivablly the IMPHD test with from the conditions the technology admitted to accomplish radioactive substrates discussed above. The procedure according to invention for the determination of the ex-vivo-activity of IMPDH is in principle not limited to the use of non-radioactive substrates or Cosubstrate for IMPDH thus.

Analyses for the distribution of MPA in full blood according to are in the therapy-relevant concentration range (about 2 to 20 mu g/ml, measured about 30 to 40 minutes after an administration of 1 to 1.5 g b.i.D. the active substance Mycophenolat Mofetil) 99.99% of the active substance in plasma contain, whereby of it 1.25% are solved in plasma water and the remaining portion to plasma proteins, predominantly HSA, bound are. About 0.01% became in the mononuclear cell parliamentary group and 0.0005% in Erythrozyten found.

The Lyse according to invention used of the cell parliamentary groups is accomplished, if necessary after suspending in plasma, in well-known way. For example the cell Lyse can take place via shock freezing in dry ice/isopropanol or liquid nitrogen and following rethawing of the cells out, via mixing with a Vortex mixer, treatment with ultrasound, or a suitable combination of these methods. The cell number contained in the parliamentary group lysierten in each case is not critical. Aptitude way should the cell number however within the range of approximately 1.10< 6> to approximately 1.10< 8>, like z. B. 1.10< 7>, cells lies.

Before execution of the enzymatic reaction the Lysat is preferably diluted with a buffer, which contains EDTA (Ethylendiamintetraacetat) and/or Allopurinol. Nichtlimitierende of examples of suitable buffer systems are trichloroethylene buffers and phosphate buffers, like trichloroethylene HCl and Kaliumphosphat with a pH value within the range of approximately 7 to 8.5 and a concentration within the range of approximately 0.005 to 0.2 Mol/l. In particular can be called: 0.1 M trichloroethylene HCl, pH 8; 0.01 M trichloroethylene HCl, pH 8,0; or 0.02 M trichloroethylene HCl, pH 8,3; or 0.1 M Kaliumphosphat, pH 7,4. Many Oxidoreduktasen, not however IMPDH are restrained by addition of EDTA. To inhibieren EDTA used in a concentration, which is sufficient, in order the activity from if necessary existing Oxidoreduktasen dependent on bivalent cations to. Thus unwanted competition reactions are prevented as far as possible to the IMPDH activity, and the formed NADH represents a reliable measure for the IMPDH activity. Suitable EDTA concentrations are appropriate for z. B. within the range of approximately 0.1 to 10 mm, like z. B. about 1 to 3 mm. In principle the procedure according to invention can be accomplished however also without admixture of EDTA. The Xanthinoxidase Hemmer Allopurinol inhibiert the oxidation from if necessary existing endogenous Hypoxanthin to Xanthin and urine acid and avoids so a falsification of the results of measurement. Reproducible results are received in particular with Allopurinol concentrations between 10 and 200 mu g/ml.

The conversion of the substrate is preferably accomplished during one period from 10 to 120 minutes, in particular 30 to 90 minutes. The reaction temperature is preferentially with approximately 37 DEG C.

The test conditions, like duration of test, suitable in each case, substrate concentration, are with the help of more suitably to determine the specialist of common preliminary tests in simple way. In each case it is to be made certain that the enzymatic conversion in the saturation region of the enzyme with substrate, D. h. in a substrate concentration range, in that substrate consumption is accomplished and/or. the product formation linear runs.

The IMPDH catalyzed reaction can be stopped in conventional way, for example by addition by acid, cousin or an organic solvent or by rise in temperature. The addition of an acid is most suitable. The addition of an aliquot of concentrated perchloric acid (HClO4) is in particular preferential. By further addition of perchloric acid and heating the reaction beginning up, for example on temperatures within the range of 80 to 120 DEG C, like z. B. 100 DEG, acid-catalyzed splitting of the N-glycosidischen connection of XMP takes place.
EMI16.1

The Xanthin formed thereby can be in an appropriate way quantitatively determined. Particularly preferentially one accomplishes the Xanthinbestimmung by means of HPLC (High performance liquid Chromatography) - analysis. In principle however also different usual measuring procedures can be used for quantitative regulation.

The evaluation according to invention preferred of the procedure which is based on those HPLC analysis of XMP is more near described in the following section. Outgoing of it it did not prepare to evaluate the specialist any difficulties modified procedures in similar way.

During the evaluation it is to be differentiated, whether the IMPDH activity in mononuclear cells a containing parliamentary group is to be determined, also the different cellular components of the blood test contains (total cell parliamentary group) or whether, for example with one with IMPDH inhibitors treated patient, who is parliamentary group who can be examined freely from Erythrozyten, Granulozyten and Thrombozyten, in particular free from Erythrozyten.

Determination of the IMPDH activity in a defined volume of a total cell parliamentary group (WBC activity):

EMI17.1
whereby f stands for a dilution factor, which amounts to for example 5, if 1 volume. WBC with 4 volume. Trichloroethylene EDTA Allopurinol buffer is diluted. DELTA XMP is calculated by after 60 and/or. 30 minutes of response time formed XMP quantities:

▲ top EMI17.2

From the WBC activity again the IMPDH activity in a defined volume full blood can be determined:

EMI17.3
whereby HC stands for Hämatokrit [%].

In full blood of healthy persons the IMPDH activity is predominantly located in leukocytes. The Vollblut Assay made possible therefore also the computation ?apparenten? specific activity in leukocytes:

EMI17.4

A differentiation into further Subtypen (Lymphozyten, Monozyten etc.) is in principle likewise possible, required however still further knowledge of possibly existing cell-specific differences.

Determination of the IMPDH activity in a defined volume of a mononuclear cell parliamentary group (MNF):
For the characterisation of the IMPDH activity in Lymphozyten of patients, who become with an IMPDH inhibitor during a longer period therapy ore, the regulation will be preferably accomplished with mononuclear cell parliamentary groups (MNF). The activity in the measured volume MNF computes itself then as follows:

EMI18.1
whereby f is defined as above. From this then the specific MNF activity can be calculated:

EMI18.2

A further the subject of the available invention is a procedure for the therapeutic monitoring of IMPDH Inhibitorbehandelten patient, whereby one determines the IMPDH activity in a blood test of the patient in the way described above. This procedure is in particular applicable for the individual dose optimization of an IMPDH inhibitor. One determines the IMPDH activity in the blood of a patient with differently high dosages of the IMPDH inhibitor and determines so the dosage of the IMPDH inhibitor optimal regarding the dose efficiency ratio determined. In addition one can intend given dosage the concentration of the IMPDH inhibitor in the blood, in particular in the plasma of the patient, for everyone the patient.

P7 A further the subject of the available invention is a procedure for the monitoring of the immunsuppressiven status of IMPDH inhibitor treated patients, whereby one determines the IMPDH activity above in a blood test of the patient as described. This procedure is in particular applicable with ~~cancer patients~~ and organ transplant ion patients. Preferably the procedure assigned with patients, who are treated with at least one IMPDH inhibitor or became, selected is under 49-57 ~~Mycophenolat mofetil, Mycophenolsäure, Tiazofurin, Ribavirin,~~ Mizoribin or VX-497, in particular under Mycophenolat mofetil and Mycophenolsäure or derivatives of the Mycophenolsäure, like z. B. Mycophenolsäureestern, which are hydrolyzable under physiological conditions. Examples of according to invention IMPDH activities of CellCept TM, determined with the help of the procedure - treated patient is summarized in the following tables 2, 3 and 4.

Table 2

Assay in full blood
EMI19.1

Table 3

Assay in mononuclear cell parliamentary group
EMI19.2

Table 4

Assay in Erythrozyten
EMI20.1

Finally the available invention concerns an analysis kit for the execution of the regulation methods according to invention, comprehensively the substrates necessary for the regulation procedure and if necessary Cosubstrate as well as if necessary further reagents to the proof from the substrates and/or. Cosubstraten formed reaction products.

Short description of the figures:

Fig. 1 biosynthesis of guanine Nucleotiden. Ribose-5-phosphat is converted over 12 steps into IMP. HGPRT stands for Hypoxanthin guanine Phosphoribosyl Transferase.

Fig. 2 schematic representation of the distribution of Mycophenolsäure between Lymphozyt (L) and plasma (P).

Fig. 3 schematic representation of the work routine for the determination of the IMPDH activity in mononuclear cells.

Fig. 4 Chromatogramm from the regulation of Xanthin after chemical hydrolysis of Xanthosin 5 ' - mono phosphate; Determination of the IMPDH activity in mononuclear cells, which were resuspendiert in plasma. Reaction stop after 30 min.

Fig. 5 like Fig. 4, but reaction stop after 90 min.

Fig. 6 like Fig. 4 (Doppelbestimmung).

Fig. 7 like Fig. 5 (Doppelbestimmung).

Fig. 8 Chromatogramm from the regulation of Xanthin after chemical hydrolysis of Xanthosin 5 ' - mono phosphate; Determination of the IMPDH activity in mononuclear cells, which were resuspendiert in plasma, which contains the IMPDH inhibitor Mycophenolsäure in a concentration of 1 mu g/ml. Reaction stop after 30 min.

Fig. 9 like Fig. 8, but reaction stop after 90 min.

Fig. 10 like Fig. 8, but with samples, which come from regularly kidney transplant ion patients treated with Mycophenolat mofetil. Reaction stop after 30 min.

Fig. 11 like 10, but reaction stop after 90 min.

The following examples describe the invention, without limiting it however to it:

Example 1

Preparation for the determination of the IMPDH activity in a total cell parliamentary group from full blood

Into a Antikoagulans containing tube 7.5 is caught ml full blood and at ambient temperature or under more easily cooling with approx. 2000.g for 10 min centrifuges. The supernatant plasma is abdekantiert and those the sedimentierte cell parliamentary group extra shift-ends remainder plasma quantity with a Pasteur or a Eppendorf pipette carefully decreased. From the cell parliamentary group 2 becomes.1-1,5 ml aliquot in plastic test tubes transferred and by immersing the test tube in a Trockeneis/i Propanol mixture or a liquid nitrogen shock-froze.

After the rethawing out the cell Lysat 4 volumes become trichloroethylene EDTA Allopurinol buffer (24 ml 0.1 M of trichloroethylene, pH 8.0, 0.1 M KCl, 3 mm EDTA in 1 ml Allopurinol solution (200 mu g/ml)) admitted. To the complete cell Lyse this mixture Mi< a DP N=22> slot afterwards at the Vortexmixer and two minutes is treated with ultrasonic. With ever 1 ml in this way won cell Lysats the IMPDH activity is accomplished in Doppelbestimmung.

Example 2

Preparation for the determination of the IMPDH activity in isolated mononuclear cell parliamentary groups (MNF)

In anti- Koagulanz containing tubes are caught 20 ml full blood and with 2 volumes 0.9%iger NaCl solution dilutes (total ones.- volume.: 60 ml). In seven 15 ml centrifuge tubes, into which 3 each was submitted ml Histopaque TM - to solution, 8-9 is carefully stacked up ml the diluted blood. The tubes become at ambient temperature (approx. 20 DEG C) and 400.g 30 minutes centrifuges. By each tube the supernatant Plasmaschicht up to 0 becomes following.5 cm above the MNF removed and rejected. With a Pasteurpipette the MNF is removed. The united MNF is distributed on four new centrifuge tubes and contents of the tubes with DPBS buffer (4.0 g NaCl, 0.1 g KCl, 0.1 g KH2PO4, 0.575 g Na2HPO4, 0.5 g D-glucose, H2O bidest ad 500 ml) are filled up to 13 ml. The cells suspended carefully in this solution become with 250.g (10 min, 20 DEG C) sedimentiert, into 10 ml DPBS buffers resuspendiert and again centrifuged (250.g, 10 min, 20 DEG C). The sedimentierten cells are resuspendiert and combined in for each I ml DPBS buffers. Out of this suspension 50 is taken mu l for cell number regulation (Thoma chamber after trypan blue colouring). The cell suspension is again centrifuged, the projection is carefully removed and the cell pellet in 1 ml plasma, which was won by the same donor by Zentrifugation of full blood, resuspendiert and with 37 DEG C 5 min inkubiert. Subsequently, contents of the test tube one shock-freezes (dry ice/isopropanol or liquid nitrogen). After the rethawing out the cell Lysat with 4 volume of trichloroethylene EDTA Allopurinol buffers is diluted and 1 min at the Vortexmixer as well as 2 min is treated with ultrasonic. With ever 1 ml in this way won cell Lysats the IMPDH activity is accomplished in Doppelbestimmung.

Example 3

Enzyme Assay

Ever 1 ml cell Lysat (from 1. or 2.) in four test tubes are transferred and in each case with 10 mu of l NAD solution (16.59 mg/ml H2O; Endkonz. = 0.25 mm) as well as 10 mu l IMP solution (8.7 mg/ml H2O; Endkonz. = 0.25 mm) shifts. Contents are mixed briefly; subsequently, the tubes are placed into a Wasserbad kept at a moderate temperature on 37 DEG C. Under repeated Umschütteln two tubes each are taken after 30 min from the Wasserbad and shifted for the completion of the reaction with 0,15 ml 4 M HClO4. The two other tubes become further 30 min (total cell parliamentary group) or 60 min (MNF) with 37 DEG C left untouched and afterwards likewise with 0,15 ml 4 M HClO4 shifts.

The tubes are centrifuged (3000 Upm, 10 min, approx. 2000.g), 700 mu l of the projection are transferred into a 10 ml brown glass and 1 h to 100 DEG C is heated up. After the cooling contents are homogenized briefly and shifted with 4 M KOH (93 mu l for beginning with Lymphozyten, 83 mu l for total blood cell parliamentary group) (pH SIMILAR 2-3). After short homogenizing and centrifugation (3000 Upm, 10 min, approx. 1400.g) the clear projection will become begun in a Braunglasvial transferred and 200 mu l from this the HPLC analysis.

The flow diagram in Fig. 3 summarizes the entire work routine of the Enzymassays with MNF.

Example 4

HPLC regulation of Xanthin 5 ' - mono phosphate (XMP)

4.1. Chromatographi conditions
Column: 2 Nucleosil C18 (125 x 4.6 mm i.D, dp = 5 mu m), in row arranged;
Eluent: 4% methanol, 96% H2O (pH 1.8, adjusted with conc. H3PO4);
Flow rate: 0.5 ml/min
Column temperature: Ambient temperature
Detection: UV (lambda = 260 Nm)
Retention time: 18-20 min.

4.2. Validating the chromatographischen method

The quantitative regulation of XMP over Xanthin is validated after internationally recognized recommendations. Concentration/signal relationship is linear within the range of 25 ng/ml-5000 ng/ml (coefficient of correlation > 0.999). To the measuring to using standards of Vollblutzell Lysat are made. The concentration/signal data's pairs received after measurement of the calibration standards first for the determination of the endogenous Xanthin content are used. Subsequently, the computation of the calibration function takes place with consideration of the endogenous mirror. During measurement of the samples from the enzyme Assays additionally calibration standards and quality inspection samples are analyzed. Selectivity investigations result in that no interference with other organic Basen (adenine (z. B. of NAD), Hypoxanthin), Allopurinol or urine acid consists.

Example 5

HPLC Chromatogramme from the regulation of XMP

The Fig. 4 to 11 shows Chromatogramme, which represent the separation from Xanthin and for the quantification of Xanthosin 5 ' - mono phosphate to be used.

Fig. 4 and 5 points the Chromatogramme to the determination of the enzyme activity in mononuclear cells, which are resuspendiert in plasma. Fig. 6 and 7 shows the Chromatogramme of the same attempt, which is accomplished as Doppelbestimmung. In a parallel accomplished attempt beginning the cells in plasma are resuspendiert, which contains the IMPDH inhibitor Mycophenolsäure in a concentration of 1 mu g/ml. Fig. show the result. 8 and 9. In addition the procedure was accomplished with samples, which come from regularly transplant ion patients with stable kidney function, treated with Mycophenolat mofetil, those the medicine in a dose of 1 g b.i.D. during one period from 3 months received. For these samples representative Chromatogramme is in fig. 10 and 11 represented.

The computation of the enzyme activity took place as described above.